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BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY OCTOBER 8 1955

TABLE OF CONTENTS

The Clinical Approach to the Problem of Diabetes Mellitus EWEN DOWNIE, M.D., F.R.C.P., F.R.A.C.P. 863

The Decrease in Surgical Paediatric Death Rate IAN FRASER, F.R.C.S.I., F.R.C.S., and JOHN A. MCCREDIE, F.R.C.S., F.R.C.S.Ed. 867

Management of the Pregnant Diabetic J. H. PEEL, F.R.C.S., F.R.C.O.G. 870

Clinical Aspects of Atypical Coronary Disease KENNETH HARRIS, M.D., F.R.C.P. 874

Treatment of Oesophageal Varices in Portal Hypertension by Means of Sclerosing Injections RONALD MACBETH, D.M., F.R.C.S., F.R.C.S.Ed. 877

Potassium and Paralysis P. E. JACKSON, M.D., M.R.C.P., and C. M. OAKLEY, M.B. 881

Treatment of Chronic Lead-poisoning with Calcium Disodium Versenate A. C. MARKUS, B.M., and A. G. SPENCER, M.D., M.R.C.P. 883

Trichomonas Vaginalis Infection in the Male W. E. COUTTS, M.D., R. VARGAS-SALAZAR, M.D., EDNA SILVA-INZUNZA, M.D., R. OLMEDO, M.D., R. TURTELTAUB, and J. SAAVEDRA 885

MEDICAL MEMORANDA

Huntington's Chorea in Northamptonshire. M. J. PLEYDELL, M.D., D.P.H. ..889

Pulmonary Rheumatoid Disease. F. DUDLEY HART, M.D., F.R.C.P., and D. H. MACKENZIE, M.D. 890

BOOK REVIEWS 891

REFRESHER COURSE

The Acute Abdomen in Children. DENIS HINDMARSH, M.S., F.R.C.S., and DONALD COURT, M.D., M.R.C.P. 899

GENERAL ARTICLES AND NEWS

Biological Aspects of Disease Transmission 902

MEDICAL INDEXING AND ABSTRACTING ..904

NEW ACADEMIC YEAR 904

VITAL STATISTICS 916

MEDICAL NEWS 918

QUESTIONS AND COMMENTS 920

OBITUARY

H. M. Turnbull, D.M., F.R.C.P., F.R.S. ..913

Harold Burrows, C.B.E., Ph.D., M.B., F.R.C.S. 914

C. H. Walker, M.B., F.R.C.S. 914

Gordon Whitehead, M.B. 915

J. D. McCulloch, M.B. 915

J. L. Cochrane, M.C., M.B. 916

Frederick Melville, F.S.R. 916

LEADING ARTICLES

Sympathectomy for Hypertension 893

Lead Poisoning in Children 894

ANNOTATIONS

Insidious Coronary Disease 895

Hydrocortisone in Anogenital Pruritus ..896

Nitrofurantoin 897

X Rays in the Field 897

Muscular Cirrhosis of the Lungs 898

The Electron Microscope 898

CORRESPONDENCE

Christmas Gifts Fund Appeal. Lord WEBB-JOHNSON, F.R.C.S. 906

Prolonged Pregnancy. W. G. MILLS, F.R.C.S. 906

Foetal Distress. T. B. FITZGERALD, F.R.C.S.Ed.; F. CHARLOTTE NAISH, M.D.; HERBERT KRAMER, F.R.C.S.Ed. 907

Chemotherapy of Bacterial Infections. G. B. GIBSON, F.R.C.S.Ed. 907

SUPPLEMENT

Full Contents on First Page of Supplement

The Shortage of Private Beds 81

Inspection of Surgeries in London 82

Hospitals Contributory Schemes 82

Correspondence :

Hospital Administration in the N.H.S. H. W. S. WRIGHT, M.S.; C. GUY MILLMAN, M.R.C.S. 84

CORRESPONDENCE—*contd.*

Piperazine Hydrate in Ascariasis. J. J. MESSENT, M.R.C.S. 907

Ocular Nerve Palsy in Diabetics. J. M. MILLER, M.D. 908

Diabetes and Pregnancy. M. I. DRURY, M.D. 908

Snake-bite in Malaya. H. A. REID, M.B. 908

Malaria and Sickling Trait. S. K. SEN, M.B. 909

Leprosy. J. ROSS INNES, M.D. 909

Diagnostic Pneumoperitoneum. A. W. REID, M.B. 909

Whitfield Tradition. R. FORTESCUE-FOULKES, M.B.; M. J. F. COURTENAY, M.B. 909

Adult Education for Consultants. J. E. M. WIGLEY, F.R.C.P. 910

Vaginal Ulceration Due to Potassium Permanganate. T. G. E. WHITE, M.D. 910

Duodenal Ulcer. C. G. ROB, F.R.C.S. ..910

Varicose Ulcers. W. J. HICKEY, M.B. ..910

Milk-Alkali Syndrome. A. G. SHAPER, M.B. 910

Backache. R. BARBOR, M.B. 911

Methylpentynol. J. J. BRADLEY, M.B. ..911

Cerumenolytic Agents. J. RABINOVITCH 911

Fibrocystic Disease of Pancreas. A. C. EVANS, M.B. 911

Barbiturate Poisoning. M. S. PERIN-PANAYAGAM, M.B., and others 912

Aortic Stenosis. M. B. MATTHEWS, M.D., and W. E. MEDD, M.D. 912

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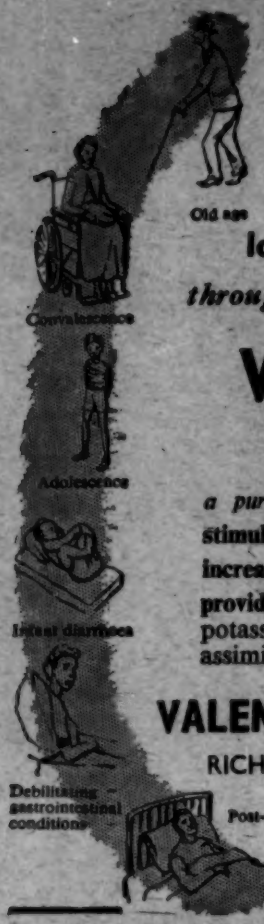

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Case Reports

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 8 1955

THE CLINICAL APPROACH TO THE PROBLEM OF DIABETES MELLITUS*

BY

EWEN DOWNIE, M.D., F.R.C.P., F.R.A.C.P.

Physician, Alfred Hospital, Melbourne, Australia

A few years ago Dr. James B. Conant (1947), in delivering the Terry Lectures at Yale University, pointed out "that scientific advance depends on two main factors—first, the development of new concepts, and secondly the development of new techniques—and that these two processes are mutually interdependent and complementary one to the other." In similar vein Dr. R. D. Lawrence (1954) said that "the twin sisters clinical observation and laboratory experiment had walked in the field of diabetes very closely hand in hand, to their mutual stimulation; the latter method is more exact, the former often more initially suggestive." It seems that, with the increasing complexity of research which is developing along so many lines, the place of the clinician can be considered in the terms of Conant's "new concept, new technique" hypothesis for the benefit of both practitioner and research worker. I feel that at times there is a tendency for clinicians, when attempting a scientific approach to a problem, to forget the role of clinical observation or to relegate it to a minor place.

The Planned Study of Disease

Shortly before his death Sir James Spence (1954) pointed out that there were two main kinds of clinical science, one of which is in danger of being overwhelmed by the other. He defined clinical science as the planned study of disease or of the phenomena of disease in human beings who are sick. He stated that this was a practical craft and that the clinical scientist must possess a particular skill necessary for collecting and systematizing knowledge. The first branch of clinical science is "the planned observation of the sequence of phenomena in that number of sick people which allows us to know the common course of the disease under study from its beginning to its end and to estimate and know the variations from that course." He suggested that this had immense practical value, for a knowledge of disease in this way forms the basis of exact therapy in professional practice. He termed this branch of clinical science "clinical cartography," because it helps the practitioner to know where he is and where he should go.

The second branch of clinical science he termed "clinical phenomenology." This seeks to study the isolated phenomena of disease, and its aim is to explain the mechanism and clinical significance of such states. He paid tribute to the enormous value of the work performed by the late Sir Thomas Lewis in establishing the precise and rational study of clinical phenomena. However, he qualified this in saying that by the mere force of his personality Lewis had so influenced clinical research in Great Britain in recent years that the study of clinical phenomena had overshadowed other kinds of clinical research, and, although the advantages derived from this influence had been great, there were grounds for believing that its dominance had led to the neglect of the planned study of disease. It could be inferred from his statements that the influence of William Osler and James Mackenzie was waning and that a return to the long-term study of the individual patient could still yield fruitful results.

The Concept of Pancreatic Involvement

The successful isolation of insulin in 1921 by Banting and Best produced a revolutionary change in medical thought and outlook on the problem of diabetes which has persisted to the present day, and it is appropriate to consider the effects of this discovery upon the cartography of the complaint. The concept of pancreatic involvement in diabetes which developed through a half-century recalls the distinguished contributions of Langerhans, von Mehring, Minkowski, Laguesse, Opie, and many others, whose observations led by induction to the conclusion that the pancreas was in some way intimately concerned with this complaint. At the time of the isolation of insulin the clinical concept of diabetes was of a static nature. Woodyatt (1909) stated "that diabetes is a disease in which the body has lost in part its ability to utilize sugar. Sugar arrives at the point where it should burn, but, failing to do so and accumulating in the blood, creates a hyperglycaemia. Disregarding accessory factors, which may play a part, we can say that ultimately the failure of sugar combustion in diabetes mellitus depends upon the lack of a something derived from the pancreas."

Within the next decade, clinical medicine came into the debt of Allen, whose scientific approach had produced a rational basis for treatment which greatly improved the outlook of many patients. In 1919 he said that "the status of the islands of Langerhans as an internal secretory organ and as the seat of the specific diabetic disturbance is now as firmly established as any fact in physiology or pathology" (Allen *et al.*, 1919). As a result of his experiments he was convinced that diabetes arose solely from pancreatic dysfunction, and considered it to be "a unified entity rather than a disjointed symptom complex."

*The Banting Lecture delivered at the University of Toronto on May 16, 1955.

The remarkable happenings of the past thirty years are still too close to view in true historical perspective. Nevertheless I think it is true that the cartography of diabetes has not kept pace with the growth of knowledge of diabetes in other spheres. The concept of a primary pancreatic failure as the reason for the development of human diabetes rests on a less secure foundation than it did, but, so far, clinical observation has failed to suggest a satisfactory alternative. The influence of various endocrine dyscrasias in varying the pattern of clinical diabetes has been established; the effect of alterations in dietary habits upon insulin requirements has been recognized, with relaxation of the rigidity of carbohydrate restriction; the existence of pre-diabetic states has been suggested; the unified concept of the aetiology of diabetes has been challenged; the influence of obesity has been recognized; the importance of heredity has been stressed; the occurrence of separate clinical types of diabetes as suggested by Lancereaux has received experimental support; while the grim realization that long-standing diabetes predisposes to premature arteriosclerosis has posed a problem second only to that of the causation of diabetes.

The unified concept of the pancreatic origin of diabetes led to the idea that the complaint when once established was incurable and that a patient was maintained in health only by living within the limits of his decreased insulin output, although this has never been proved, or by using insulin as a means of substitution therapy. Yet Banting (1929) himself quoted an early case which is of much interest. In August, 1922, a woman of 65 suffered an infected gangrene of the leg with ketosis and a high blood-sugar content. After five days of insulin therapy her urine was sugar-free, her leg was amputated, and she improved rapidly. After four months insulin was discontinued and eight months after the operation she was living satisfactorily on a free diet. For three years thereafter she remained well, dying eventually of pneumonia in 1926.

Fluctuation in Severity

In 1930 I first observed the apparent fluctuation in severity of diabetes (as estimated by variation in insulin dosage) in patients suffering with infections of various types (Downie, 1930). I also noticed disturbances in the carbohydrate utilization (as shown by variations in glucose-tolerance tests) in patients with no diabetic heredity during the course of infections (Long and Downie, 1932). With subsidence of the infections such patients showed normal glucose-tolerance curves, which remained normal over periods of some years. Since then this problem has interested me and has stimulated thoughts that perhaps there are some forms of diabetes which are not permanent throughout life but which remit or disappear under influences as yet unrecognized. The relationship of obesity to the development of frank clinical diabetes presents a similar problem. In 1939 Newburgh and Conn showed that in many patients of this type reduction of body weight to normal limits resulted not only in the disappearance of symptoms but in a reversion of the glucose-tolerance curve to normal and in some instances to an apparent cure, as the curves remained normal over many years of observation.

This raises a question whether in the cartography of diabetes reversibility of the disorder can occur apart from the conditions already recognized—namely, infections, endocrine disorders, pregnancy, and obesity. Obviously the clinical assessment must rely in the last instance on the figures obtained by a glucose-tolerance test performed under standard conditions, with due regard to previous diet and the estimation of true blood sugar. This problem has attracted relatively little interest, which is all the more surprising in view of the suggestions of Haist and Best (1941), who indicated possible ways in which clinical trials could be undertaken in an attempt to protect the beta cells of the pancreas from damage. Watson (1942, 1949) described a series of patients whom he had observed over a period of years in which diabetes seemed to subside and to recur under the influence of dietary restriction and excess.

Influence of Diet

It so happens that there has come within my experience a group of patients which not only supports the findings of Watson but which poses additional questions. As a clinician I find it perplexing to be confronted with problems in cartography to which there is, as yet, no answer. To illustrate this I propose to consider briefly some case histories taken from my experience since the war.

The first two cases are concerned with the effects of obesity. In the first case, an apparent remission occurred with a fall in weight, only to be followed two years later by a recurrence

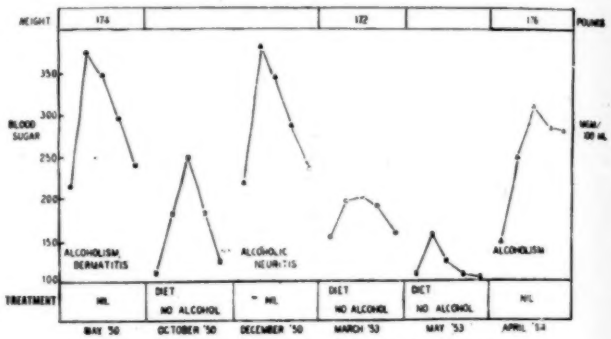

FIG. 1.—Man aged 51. No family history.

which was not associated with any gain in weight. Diabetes has persisted, and the patient has required insulin for the past six years. The second case is one of response to reduction in weight with a relapse after carelessness with diet. Symptoms recurred and subsided with weight reduction, and at least for a time diabetes has again passed into a stage of remission. The next example may possibly be related to the effects of infection. It is that of a man whose mother suffered from diabetes, and who developed typical symptoms at the age of 55 years in 1947. With dietary restriction he remained well, and in 1953 showed a normal glucose-tolerance curve after a period of unrestricted diet. Within the past year, following a virus pneumonia, he again developed symptoms, and his curve has reverted to a diabetic pattern.

The next case history is that of a man of 51 with no known family history of diabetes whose diabetic state seems to come and go with his alcoholic habits (Fig. 1). He has been an extremely heavy drinker for many years, but on two occasions within the past five years his diabetic condition seems to have subsided with periods of abstinence.

It is tempting to try to relate these findings to some cause; obesity, alcohol, or infection, and to infer that, in some way, dietary or alcoholic indiscretion or infection has played a part in determining a relapse in a susceptible subject. However, the next two examples do not permit such an explanation, as recurrence has developed for no apparent reason.

The first history is that of a man aged 56 in 1937 who was diagnosed as suffering from diabetes prior to an operation for thyrotoxicosis while in London. His father was a diabetic. He was stabilized on insulin and remained on this treatment for 10 years, when the use of insulin was discontinued because of severe and repeated hypoglycaemic attacks. He remained well, and glucose-tolerance tests were normal for the next six years. Then for no demonstrable reason he relapsed with typical symptoms of uncontrolled diabetes and has resumed insulin therapy.

The second history is that of a man of 40, not overweight, whose father and an uncle suffered from diabetes. He developed typical symptoms of the complaint in 1948. Within three months of dietary treatment and with no appreciable alteration in weight, his glucose-tolerance test gave a normal response. It remained so for at least the next five years, when he again developed symptoms with a typical recurrence of diabetes. No obvious reason has been ascertained for this.

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It is, of course, the privilege of patients to rationalize their experiences and to attribute the development of diabetes to this or that event which, in their minds, is directly related in time to the development of symptoms. Be this as it may, a sudden shock or nervous stress is often mentioned as a precipitating factor.

A man of 50, whose father and mother suffered with diabetes, was found to have symptomless diabetes when examined for life assurance (Fig. 2). With dietary treatment his glucose-tolerance reverted to normal and remained so for over two years. Then, following a period of severe financial stress, he developed symptoms for the first time in his life and again showed a typical diabetic response to a glucose-tolerance test. Another man, aged 62 years, with no family history of diabetes, developed

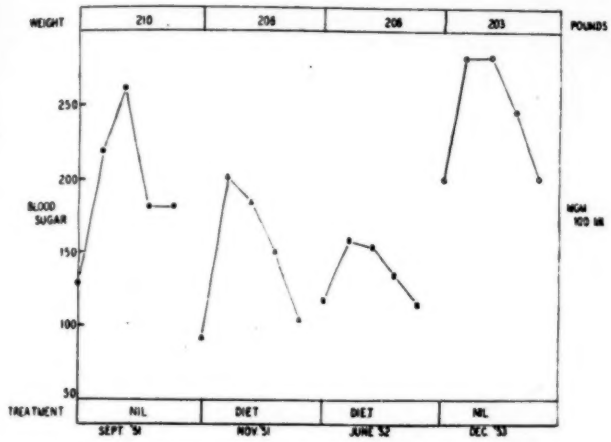

FIG. 2.—Man aged 50. Family history, two cases.

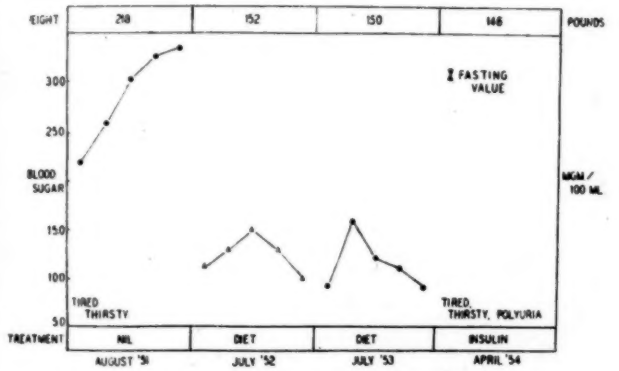

FIG. 3.—Man aged 62. No family history.

symptoms in 1951 (Fig. 3). He had been overweight for many years, and with reduction of his weight to normal his diabetes passed into a remission for over two years. Then, following a long period of intense domestic stress, he again developed symptoms and now requires insulin for satisfactory control.

All these patients have been maintained on a mild carbohydrate restriction (between 150 and 200 g. daily) throughout the period of observation except for one week prior to the performance of glucose-tolerance tests, when their intake has been raised to approximately 300 g. daily. It seems significant that the majority of these patients have shown clear evidence of a strong hereditary influence. This surely poses a question of considerable clinical importance in these days of diabetic detection drives, for if attempts are made to discover the diabetic patient in his earliest symptomless phase, what advice is to be given by the physician?

A Technique of Value

Before proceeding into this controversial field I wish to refer to a technique which may well prove to be of value to the physician confronted with such problems. Fajans and Conn (1954) have used a cortisone-reinforced glucose-tolerance test for detecting disturbances of carbohydrate metabolism that are not revealed by the standard tests in common use. I have recently applied this technique, not to the problem of detecting unknown diabetes, but to patients who have developed diabetes and have subsequently passed into remission. A few examples are considered briefly.

A child of 6 years, with a family history of diabetes in a maternal grandmother and a paternal grandfather, developed diabetes in 1950 and showed a typical response to a glucose-tolerance test (Fig. 4). She was controlled with dietary restriction and insulin, and responded quite satisfactorily to treatment throughout 1951 and 1952. Blood-sugar estimations during this period were usually within normal limits. Early in 1953, with some trepidation, I discontinued insulin and maintained a strict dietary regime. Her blood-sugar values remained within normal limits and her urine tests showed no sugar. Fascinated by this, I performed a glucose-tolerance test after a week of completely unrestricted diet. The result was normal. Dietary treatment was resumed, and six months later another test was performed after unrestricted diet, and it was normal. A year later it was still normal, and a cortisone-reinforced test was also normal.

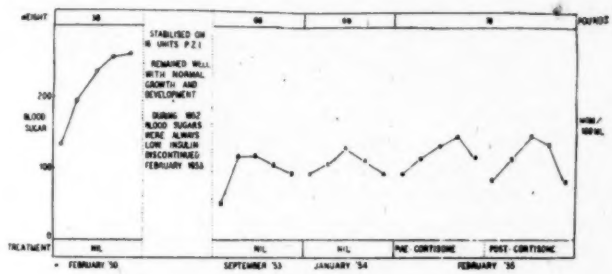

FIG. 4.—Girl aged 6. Family history, two cases.

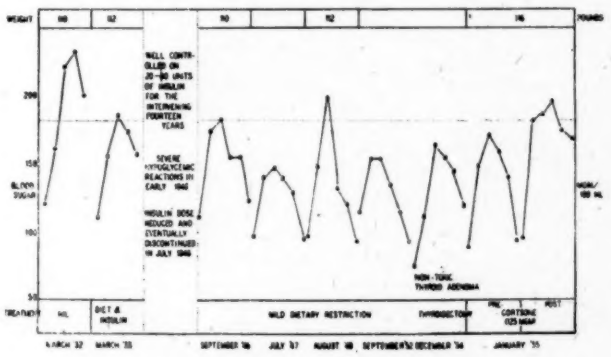

FIG. 5.—Woman aged 27. Family history, one case.

This child is unique in my experience. She is normal in height and weight for her age (10 years), but I am still fearful that when she approaches puberty diabetes will recur. Had I a preparation of purified growth hormone I would be tempted to use it prior to a glucose-tolerance test in an attempt to resolve my doubts.

In 1933 I saw in consultation a woman aged 27 (Fig. 5) whose father had suffered from diabetes. Two years previously she had felt tired, thirsty, and had lost weight, and glucose-tolerance tests revealed diabetes. She was stabilized with diet and insulin, and remained satisfactorily controlled for the next 14 years. She then came under my observation because of repeated hypoglycaemic attacks which had developed only within the previous six months. Within the next six months I discontinued insulin, and with dietary treatment alone her blood sugar values were always normal. Accordingly I carried out a glucose-tolerance test after a short period of unrestricted feeding, and it was normal. For the past eight years she has followed a mild dietary restriction with a daily intake of carbohydrate of approximately 175–200 g. Her glucose-tolerance tests have been normal, even in 1952, when she had a severe throat infection which lasted several weeks and failed to respond to antibiotic therapy. Within the past few months a glucose-tolerance test was quite normal, but with cortisone reinforcement a typical diabetic curve was found.

Fajans and Conn investigated six mild obese diabetic patients, all of whom, after weight reduction, exhibited normal glucose-tolerance curves. With cortisone reinforcement they all showed a significant deviation from their previous response. I have recently had the opportunity of observing two obese patients whose symptoms subsided with weight reduction and whose glucose-tolerance curves returned to a normal pattern. Each subsequently showed a reversion of the curve to a diabetic pattern, although there was no alteration in weight or other determining factor. These two men were studied with cortisone-reinforced glucose-tolerance tests and gave different responses.

The first example is that of a man aged 36 with no known family history of diabetes (Fig. 6). He has always been heavy, and on discharge from the Army in 1946 weighed 280 lb.

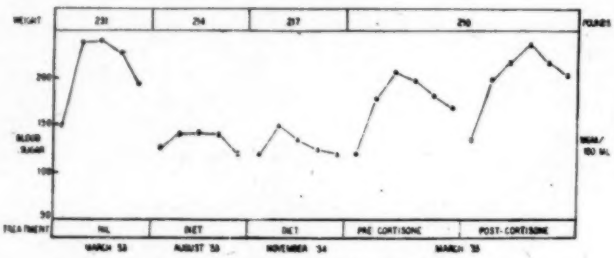

FIG. 6.—Man aged 36. No family history.

(127 kg.). His height was 6 ft. 4 in. (193 cm.). In 1952 he developed definite symptoms of diabetes, and a glucose-tolerance test gave a typical response. His weight was 252 lb. (114.3 kg.). Within four months of dietary restriction his weight fell to 210 lb. (95.3 kg.) and his glucose-tolerance test was then normal. He remained on a mild carbohydrate restriction, and 15 months later the curve was still normal. A further review early this year showed that the curve had changed to a diabetic pattern. A cortisone-reinforced test was then performed and showed identical figures.

The second example is that of a man aged 44 whose father had suffered from diabetes. In 1953 he began to feel tired, and a glucose-tolerance test gave a typical diabetic response. His weight was 205 lb. (93 kg.) and his height 5 ft. 6 in. (167.3 cm.). With dietary treatment his weight fell to 176 lb. (79.8 kg.) in a period of seven months and the glucose-tolerance test returned to normal. Subsequently, for no obvious reason, it changed to a diabetic pattern, and with cortisone reinforcement a significantly greater deviation from normal was observed.

Finally, in 1952 I treated a girl of 12 years who presented with acute symptoms of diabetes which had been present for a few weeks. She was easily controlled with insulin and diet, and has remained well ever since. There was no family history of

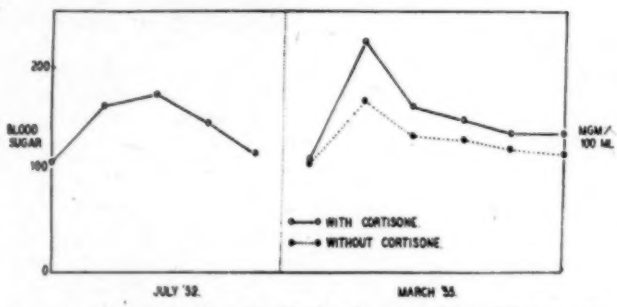

FIG. 7.—Girl aged 12. Identical twin sister has diabetes, controlled by 110 units of insulin daily.

diabetes, but the patient was an identical twin. Her sister was given a glucose-tolerance test in 1952 and showed a normal response (Fig. 7). This twin has remained well and symptomless ever since, and a recent test was still normal, but a subsequent cortisone-reinforced curve showed a significant deviation.

Four of these patients who have been investigated with cortisone-reinforced glucose-tolerance tests have had clinical diabetes. In none of them has there been any other clinical abnormality at the time of onset, and in all of them diabetes seems to have subsided for an appreciable period. In the four diabetic patients, cortisone reinforcement failed to alter the pattern of the curve in two, while a significant change was observed in the other two. The fifth patient, an identical twin of a diabetic sister with no clinical evidence of diabetes, shows a significant response to cortisone stimulation.

A Personal Concept

The concept I have developed from this experience is that of a dynamic fluctuating state rather than one of a static and permanent disease entity. For the present, reversibility of diabetes must remain a clinical dream. Yet, if we reflect upon the histological pattern of the diabetic pancreas and on the work of Wrenshall and his associates (1952), it must be realized that at least in some instances of diabetes of long standing the beta cells are obviously neither dead nor functionless. This leads to the speculation that they may be under the influence of some agent which, while allowing them to live as sick cells, is not lethal for them. One of the great experiences of my clinical life has been to witness the effect of cortisone therapy on the course of rheumatoid arthritis. Joints which, fixed, gnarled, and functionless, were regarded as the end-result of some noxious influence, have been transformed, causing a complete alteration in our concept of the nature of the complaint. With such thoughts in mind, I wonder whether something as yet unknown may some day be capable of reversing the changes in sick pancreatic cells.

It is permissible to speculate that in the cases just described an oscillatory state of bodily homoeostasis has been disturbed by factors beyond our present knowledge. The effect of carbohydrate restriction in compensating for this disturbance may represent no more than an adjustment to an altered equilibrum which may be influenced by any one of several stimuli that are not necessarily related to one another. The stimulus to the development of diabetes in a susceptible individual, like the clinical pattern of the disease at different periods of life, does not seem to be the same in all cases.

Heredity

In a significant number of the patients I have studied there is the common factor of heredity. I have formed the opinion that this is of greater frequency than can be disclosed by figures obtained from the interrogation of patients known to be suffering from the complaint. It is not uncommon to observe diabetes appearing in a child or a young adult whose family history is quite clear. Then, years later, the father or the mother or some other close relative will develop diabetes at an advanced age in life. A few years ago, Harris (1951) pointed out that various hypotheses have been put forward at different times to account for the observed familial distribution. Levit and Pessikova (1934) suggested that the condition could be regarded as an irregularly manifesting heterozygous character, while Pincus and White (1933) put forward the hypothesis that diabetics were homozygous for a relatively common recessive gene. Harris (1951) pointed out that there were certain features of the familial distribution which were inconsistent with both of these views. He suggested that sometimes the late onset and less severe forms of the disease may be heterozygous for a gene, which in homozygous form leads to the early onset and more severe type of case.

The problem of heredity is one of cartography, and is not likely to be solved by laboratory studies of phenomenology alone. My colleague and mentor, Sir MacFarlane Burnet (1953), has pointed out the importance of three new subsciences—population genetics, biochemical genetics, and microbial genetics—all of which are likely to have very great influence on the future as well as in the future. He gives as an illustration the condition of congenital amentia which arises because of the genetic absence of an enzyme (phenyl pyruvic oxidase) in body cells. This he regards as an example of biochemical genetics which he thinks may well emerge as the master biological science of the future.

He suggests that in the last analysis all the changes produced by genes are expressed through a series of chemical reactions and that there is a growing belief that in some way each gene controls no more and no less than a single type of enzymic action. If the generalization "one gene—one enzyme" is finally established it will represent one of those great simplifying concepts like the idea of evolution by natural selection or the quantum theory.

This view, when considered with Harris's suggestions, can be related to the problem of human diabetes. Some few years ago Himsworth (1949) suggested that diabetes should be regarded as a symptom-complex rather than as a disease *sui generis*. - Hyperglycaemia, the common factor in all diabetes, may not necessarily arise from the same cause in every diabetic patient. Likewise, no satisfactory attempt has yet been made to reconcile the arteriosclerotic complications of long-standing diabetes to genetic defects, yet no clinician of experience can deny that this is an inexplicable problem. For many years attempts have been made to relate it to adequate control of diabetes as measured by maintenance of normoglycaemia. It falls within the knowledge of us all that, although strict control of diabetes seems to offer some protection against vascular damage, it is by no means proved that it does so in all cases. This may be related to different types of diabetes arising from insulin deficiency or from disturbed utilization, or to genetic influences suspected but as yet unproved.

Conclusion

Medicine in the present day is becoming increasingly indebted to the developments of science and has need to keep pace with the ever-expanding frontiers of knowledge which are opening before it. Yet it seems that the sense of perspective, so necessary to any critical appraisal of new knowledge, must constantly be related to clinical experience. Cawadias (1953) has said that "the history of medicine has shown that, whenever medicine has strayed from clinical observation, the result has been chaos, stagnation, and disaster." This represents a serious challenge to those of us charged with the management of diabetic patients. The clinical concepts of diabetes at present rely heavily upon the interpretation of the glucose-tolerance test to determine the existence of this nebulous entity, diabetes, which, in the words of F. G. Young, cannot be precisely defined. The twin sisters clinical observation and laboratory experiment must obviously continue to walk together very closely, the one to produce concepts of reversible or curable diabetes, the other to produce techniques which, applied to the patient like Mackenzie's polygraph, will enable us to plot the course of the disease with ever greater accuracy. The need for long-term genetic studies of diabetes of fluctuating intensity must surely lead to greater understanding, while the development of new techniques which, for example, could provide an easy and rapid estimate of pancreatic, adrenal, and pituitary activity, would place into the hands of the physician weapons with which the problem of diabetes might be solved.

Surveying the development of our knowledge of this most fascinating and baffling subject, the secret of diabetes mellitus, we are reminded of the contributions of the great men who have passed. Of these Frederick Banting, whose memory we honour this day, must serve as an example of one who combined a concept with a new technique and so placed the world in his debt. The stimulus of his discovery is still felt throughout the world, while millions of patients owe their health and existence to him. It can be truly said that he has joined

> The choir invisible
> of those immortal dead who live again
> in minds made better by their presence, live
> in pulses stirred to generosity,
> in deeds of daring rectitude, in scorn
> for miserable aims that end with self,
> in thoughts sublime that pierce the night like stars
> and with their mild persistence urge man's search
> to vaster issues.

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THE DECREASE IN SURGICAL PAEDIATRIC DEATH RATE

BY

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The decrease in the mortality rate from various diseases and operations is an insidious process. Although one may suspect it, it is dramatically evident only when definite figures are produced. Coincident with a reduced death rate there is always a lowered morbidity rate, and in proportion to the latter there is an increased turnover in the bed state due to the shortened time in hospital. Unfortunately, other factors have crept in to counterbalance this, so that the waiting-list for the average hospital is greater to-day than it was 10–20 years ago; but a National Health Service, a Welfare State, and other personal economic factors have, in the meantime, come to play their part in the life of the private individual.

In the Royal Belfast Hospital for Sick Children the figures seemed striking enough to warrant publication. They probably represent merely what has happened in all similar institutions. The number of surgical beds in the unit has remained fairly constant. Two seven-year periods were selected, 1931–7 and 1947–53.

A series of those diseases which recur with sufficient frequency to warrant classification has been selected, and the results are shown in the Table and Fig. 1.

It may be argued that with some of these—for example, cleft-palate and pyloric stenosis—where the disease and the time for operation are under the control of the surgeon, the death rate should be nil. On the other hand, with others, such as burns, trauma, and the toxic conditions, the outlook must depend to a certain extent upon the insult the body has received in the way of shock and infection before treatment was started. Fig. 2 shows that there has been a steady decrease in the average age of death, largely due to the fact that surgery is being carried out for congenital abnormalities—that is, oesophageal atresia—which, in the first period, did not

even enter the surgical ward. Fig. 3 shows that for one week spent in hospital to-day one month was so spent in the period 1931–7. This is further proof that a decreased morbidity has accompanied the all-round decrease in mortality.

Surgical Ward Mortality Figures

Disease	1931–7			1947–53		
	Admissions	Deaths	% Mort.	Admissions	Deaths	% Mort.
Acute appendicitis and complications	1,104	45	4·1	3,059	8	0·26
Intussusception ..	210	29	13·8	357	6	1·68
Burns	573	58	10·1	1,442	12	0·84
Injury	1,577	21	1·3	2,807	24	0·85
Cleft-palate and -lip	202	10	4·9	427	5	1·17
Acute infections (cellulitis, osteomyelitis, arthritis, septicaemia)	887	25	2·8	1,939	2	0·10
Pyloric stenosis ..	67	8	11·9	252	2	0·8

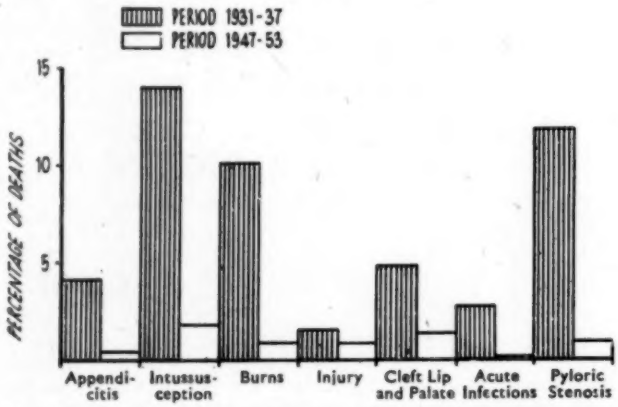

FIG. 1.—Showing the decrease in surgical paediatric death rate in various conditions.

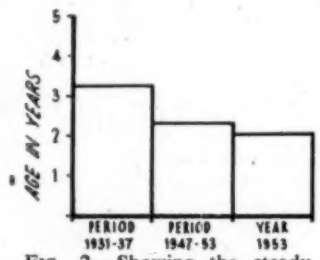

FIG. 2.—Showing the steady decrease in the average age of death in children undergoing operation.

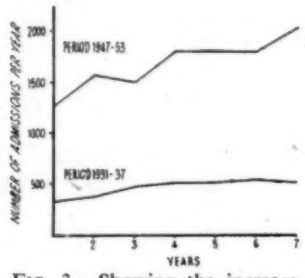

FIG. 3.—Showing the increase in the number of admissions to hospital.

Acute Appendicitis and its Complications

What are the factors that reduced the deaths from 1 child in 25 to 1 in 400 (see Table)? Are parents more enlightened or has the doctor become more skilled in diagnosis? Actually the number of children admitted to hospital with a perforated appendix and local abscess formation or peritonitis is still very high, although perhaps not so many are admitted almost moribund with practically no pulse, with a distended abdomen, and vomiting—the picture of complete ileus. With a disease which, unfortunately, presents without fulminating signs and symptoms, in an organ which can be found in many and varying anatomical situations, the onset cannot be expected to follow always the classical textbook picture.

In the child the appendix has a small lumen, the transverse colon a poor omentum; and, since the patient is often inarticulate and not intentionally uncooperative, I am afraid that the perforated appendix, even with the most intelligent co-operation of parent and doctor, will still appear.

The surgeon has changed little in his dexterity or in his tools. The incision and operative manœuvres are much the same. There is still the problem of whether to operate in the presence of an appendix abscess or appendix mass when the patient is not showing signs of disordered peristalsis. There are those, perhaps, who are capable of differentiating these two conditions—the perforated appendix with local abscess and the gangrenous appendix clothed with a mass omentum. Both are rare in the child as compared with the adult: so that it is doubtful indeed if there is the same possible justification for delay in operating in a child. Having operated, there is the second problem: when is it justifiable simply to drain, and when to open up fresh tissue spaces, especially retroperitoneally, to have the satisfaction of removing the gangrenous appendix? Some people lack the moral courage to admit that they have failed. A chief should always give commendation rather than create the impression that if he had been there he would not have failed.

Finally, what degree of peritoneal infection requires drainage and what can the body resistance deal with?

The secondary abscess still does occur sometimes in the pelvis, in the left iliac fossa, in a subphrenic space, or occasionally above the old abscess. It does not seem to occur more frequently in the undrained than in the drained case—perhaps it is more common in the drained case.

What are the factors now saving the children with ileus and peritonitis who formerly often died? Probably in order of value they are: (1) Parenteral fluids, especially intravenous glucose and saline; in addition, hyaluronidase subcutaneous, rectal, and ordinary subcutaneous transfusion still have an occasional place. These are first-aid measures, and tide over the short period till blood, plasma, and balanced electrolytes are available. (2) Gastric suction with a Ryle tube to decompress the paralysed gut, to allow it to rest and to permit it to recover its elasticity and peristalsis. (3) Selective anaesthesia, non-irritating to the lung, short-acting, but with adequate relaxant of proper duration. (4) Antibiotics—possibly in order of value, chlortetracycline or oxytetracycline, streptomycin, the sulphonamides, and penicillin. (5) Early ambulation. (6) Vitamins, especially vitamin C for wound-healing and vitamin B if the patient has been long on any of the "mycins" or "cyclines." (7) The haemoglobin kept constantly over 80% and the blood pressure maintained at a constant level by noradrenaline or other method. (8) Sedatives, especially morphine (at one time greatly disproved). (9) Avoidance of all forms of parasympathetic stimulation—for example, pituitary "pitressin," carbachol, etc.

A child should never die from paralytic ileus if it can be kept alive long enough for normal peristalsis to recover. Gross states that no child has died from appendicitis in the Boston Children's Hospital in a recent seven-year period. During 1953 we had one death due to an ether convulsion. The child recovered from the anaesthetic, but was decerebrate until he died some seven days later.

Intussusception

This condition is now better recognized by the parents, and, with an increasing number of baby clinics, paediatric units, and postgraduate lectures and courses, the medical profession is better prepared.

Most hospitals now have a 24-hour *x*-ray service and all the facilities for diagnosis. The Welfare State, with its ambulance service and the domiciliary consultation scheme, has put free paediatric consultant advice into every home. Why, therefore, are there any deaths from intussusception? The deaths occur nearly always because the patient reaches surgical help too late. In some cases it is due to distance: the household is isolated miles from medical help or the onset has coincided with an epidemic of diarrhoea or dysentery. In other cases the child has previously had rather similar attacks of colic and wind which had been diagnosed as "teething"; consequently, when the genuine intussus-

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ception does appear it is missed. In many cases no one is to blame, since the sequence of events has not shown the classical picture.

Recently, in a series of 200 cases treated in this hospital, blood was present in less than 80%—that is, 20% did not show the classical blood-stained stool, without which many will refuse to diagnose the condition. In a recent case the apex of the intussusception was in the rectum without obvious blood having been passed. Of the 200 cases analysed, 142 had symptoms of less than 24 hours, and in this group there were no deaths; 28 had symptoms between 24 and 48 hours, and of these 8 died (29% mortality); while 19 had symptoms exceeding 48 hours, and of these 7 died (37% mortality). It would seem that we have 24 hours in which to diagnose an intussusception and save a child's life. In this series 71% were diagnosed within that period—that is, about one-quarter were missed. It is to this group of very ill children that modern surgery has something to offer. Correct preparation of the patient and balancing of his fluid and electrolytes is time well spent. The surgical technique basically depends on (1) the removal from the body of gangrenous tissue; (2) a safe surgical technique which avoids peritoneal soiling; and (3) a final state where no external uncontrolled drainage of small-gut contents is allowed to discharge on the surface or produce skin irritation. The sick child cannot tolerate the loss of its valuable intestinal content nor can it stand digestion of its skin.

Immediate anastomosis is to be preferred after resection when possible; or, if not possible, re-establishment of the continuity of the gut must not be long delayed. Selective anaesthesia and the "polythene" tube for intravenous infusion make the post-operative period a less anxious time and more easily controlled.

Burns

The mortality rate has been reduced from 10.1% to 0.84% (see Table). Figures can be made to prove anything, not necessarily the truth. The addition to the staff of a plastic surgeon and a physician responsible for the metabolic side of burns, together with the formation of a specialized burns unit, might be said at first sight to account for this improvement. Analysing this further, we also see another factor. In the early series burns were chiefly from the urban area of Belfast and adjacent rural districts. With the development and centralizing of a burns unit we naturally draw from a large area—a radius of 100 miles—but against this is the fact that the children who reach us are those that are fit to travel and that the moribund have died elsewhere. It is just as sensible to compare the mortality rate in a F.S.U., F.D.S., or C.C.S. with a base general hospital. The deaths are filtered off at each stage.

Dupuytren's six-grade classification of burns has been discarded after holding the field for almost 200 years. Now they are graded into two simpler categories—(1) skin damaged but recoverable, and (2) skin lost and irreplaceable. In group (1) the treatment is to prevent the damaged skin deteriorating into complete skin loss. In group (2) provision of a skin cover as soon as feasible is the only treatment.

Picric acid in water, tannic acid solution, tannic acid jelly, gentian violet, petroleum wax, ambrine, Bunyan's bags, pressure bandages with cotton-waste, marine and synthetic sponges all spring to the mind as milestones along a very troublesome journey. They show by their number and transitory nature how unsatisfactory and impracticable on the whole the treatments have been.

To-day the techniques are fewer, but the principles are based on a sounder concept: (1) Correct the haemoconcentration by replacing the lost plasma. (2) Control infection by antibiotics—the large exposed surfaces form a perfect Petri dish for every invading organism. (3) Give a cover to prevent reinfection. This cover may be (*a*) by skin in any of the various forms of skin transference—whole skin, half-thickness skin, complete skin cover, or islands of skin cover; (*b*) by coagulation—a crust or scab, produced by the drying and exposure of the natural protein exudate; and (*c*) by some textile material cover—tulle gras, petroleum jelly, or net, or other protective cover where (*b*) is not a feasible method.

Thus plasma, blood, antibiotics, cetrimide, skin cover, rapid healing, lack of dressing, and abolition of pain have transferred the problem and treatment of the burnt child from being an agonizing nightmare to both doctor and patient to being a well-balanced and surgically staged procedure, in which the physician and the anaesthetist have a large share in the successful result. The anaesthetist, with rectal thiopentone, can allow the dressing to be done painlessly; and with hypotensive drugs vast areas can be denuded, giving large areas of skin of regular thickness. As in other cases, the surgeon's tools have been of less importance that the physiological outlook which now controls their use.

Injury

The death rate from injury is a little lower, but it does not show the dramatic fall of the preceding examples. Here is a problem in which prevention is the only cure. With the tempo of life increasing, with the greater number of private cars and public vehicles on the roads, with home help and home conditions less easy, and with more parents engaged in gainful labour, children have less protection and the areas into which they stray are more dangerous. This is one of the aspects of life not adequately protected by the Welfare State. Therefore, accidents under these conditions must increase. The motor-car and the internal combustion engine are more lethal weapons than a "tommy gun." The "knock-down" accident and the "run-over" accident should be segregated. With a child the "knock-down" accident carries a smaller mortality. The child's body weight is brushed aside by a vehicle and he has a shorter distance to fall. An adult 6 ft. (1.8 m.) tall and weighing 14 st. (89 kg.) offers a large bulk of resistance, so that when his head strikes the ground—through an arc of 6 ft.—it does so with considerable force. It is a constant surprise that head injuries in children in actual fact do so well. The "run-over" accident in the child, on the contrary, is a serious problem—the frail bony cage offers little resistance except to the lightest of vehicles.

Fatal injuries must arise. One cannot damage an organ at its hilum, be that lung, liver, kidney, or spleen, without producing catastrophic haemorrhage, which allows little or no time for even the most efficient first-aid service to be of any help. Injury at the periphery of these organs, on the other hand, may give the surgical team the short period of grace necessary.

Thus, although surgical skill may have increased along with surgical courage, thanks to the experience and training of a recent war, and although a blood transfusion service is immediately available, the problem is still mostly one of time and resuscitation.

The figures given in the Table, again, are not a true indication of the effects of trauma and road accidents, since they do not include those admitted direct to the mortuary. They tell of the deaths of those patients reaching hospital alive, and so do not reflect the value of modern resuscitation. One should include those admitted to the mortuary; then and only then will we be able to see whether trauma and its effects is on the increase or not.

Cleft-palate and Cleft-lip

The value of modern surgery is really reflected in the results shown in the Table. The plastic surgeon is able to centralize his cases, the theatre technique can be standardized, and nursing can be carried out according to one man's plan and not with modifications to please the wishes and whims of several operators—each sure in his own mind that his is the only method. Correct timing of the operation and stages, intratracheal anaesthesia (originated by Ivan Magill) and an electric sucker, physiotherapy, and antibiotics are all links in the surgical chain. They have allowed the operation to be carried out with the utmost care, in a bloodless field, and with a dry pharynx. Since 1950 we have had no deaths from this operation.

Acute Infections

Towards the end of the 1931–7 period the sulphonamides were just coming in, with a dosage not fully understood, with some dangers overemphasized and others not realized. When one remembers the horrible problems of septicaemia, arthritis, and osteomyelitis, a total of 25 deaths was not larger than one would expect. In 1947 penicillin was becoming cheaper and more fully available, and in the intervening years its successors have kept appearing with gratifying regularity. In addition, all through this second seven-year period we have had the steady support of readily available blood transfusion—available in quantity to sustain the patient until the specific remedy was found and had time to take effect.

Not only did this disease group almost vanish, to a mortality of one death in a thousand patients, but in the second seven-year period there were double the number of admissions ; and an acute infection which in the first period took days, weeks, or even months—for example, in the case of bone diseases—to clear up now suddenly disappears after a few days' treatment with one of the "wonder drugs." This has been accompanied, too, by the almost total disappearance of gross subsequent deformities.

Osteomyelitis suddenly changed ; from a septicaemia with simple or multiple local manifestations, it became a disease with a sterile blood stream. The bony lesions still showed necrosis—perhaps a sterile necrosis—till the suitable combination of decompression of the bone by minute drill-holes and the use of an antibiotic was established.

Perhaps another seven-year period 20 years from now may not show as good results if a population of antibiotic-resistant patients has by then been produced. Or will there still be bigger and better spectra of antibiotics ?

Congenital Pyloric Stenosis

In surgery the best results are obtained from the relief of mechanical obstructions, and this condition is a perfect example. With suitable pre-operative preparation of the patient, with adequate hydration, with a basal narcotic—for example, rectal thiopentone—with the operation performed under a local analgesic, with a transverse incision, and with the abdominal wound closed by a suitably non-absorbent suture—for example, nylon—a simple surgical technique can be evolved. Staining and shock are avoided. The patient should be awake at the end of the operation. There is no fear that the abdominal wound will burst apart, and yet the child is given full freedom. The operation should have a mortality of nil, but the missed diagnosis, the neglected case, and the wasted child with intercurrent disease still appear to make the operation a hazardous procedure, no matter how well carried out.

Summary

The death rates from some of the more frequent surgical conditions are compared in two seven-year periods, 1931–7 and 1947–53. Some of the factors responsible for this improvement are discussed.

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Children starting school at the age of 5 have, on average, five of their teeth missing, decayed, or filled, said Miss Pat Hornsby-Smith, Parliamentary Secretary to the Ministry of Health, when she opened the new Stroud Green Dental Centre at Croydon on September 28. There was no doubt, she said, that one of the main causes of the increase in dental decay since the end of the war had been the greatly increased consumption of sweets. Children should not eat sweets all day, and teeth should be brushed or the mouth rinsed after they had been eaten. To clean their teeth before retiring and send them to bed with a mouthful of sweets or biscuits was asking for trouble.

MANAGEMENT OF THE PREGNANT DIABETIC*

BY

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Problems relating to pregnancy in diabetics have in the past two decades aroused a greater interest and achieved a greater importance than the frequency with which pregnancy and diabetes are associated in clinical practice appears to justify. Some years ago Dr. W. G. Oakley and I had occasion to collect information on this subject in Great Britain. We collected details of all the cases treated in 26 different teaching centres, where they tend to concentrate. Over a seven-year period there were only 458 diabetics cared for during pregnancy, which works out at about three cases per annum in each hospital. At my own hospital, King's College Hospital, we have a very large diabetic clinic under the direction of Drs. R. D. Lawrence and W. G. Oakley. We have therefore a great concentration of clinical material, and for many years now I have looked after 20–30 cases a year. I shall quote from my personal experience of a series of 298 pregnancies in diabetic women seen during the last 11 years.

Why are we, as obstetricians, taking a so much greater interest in this subject ? I think it is because in this relatively small group of patients we encounter problems relating to foetal size, placental function, intrauterine foetal death, hydramnios, toxaemia, congenital foetal abnormalities, and neonatal mortality. The solution of any or all of these problems in the diabetic will, we hope, help us to understand more about foetal physiology and pathology in general. But knowledge is slow to accumulate, and there are many riddles still awaiting elucidation before we can explain fully why for the diabetic woman reproduction is such a relatively unproductive enterprise.

The control of maternal diabetes by means of insulin and dietary measures has reduced enormously the maternal risks during pregnancy. The maternal mortality is now as little as 1% or less—0.4% Joslin (1946) —compared with 45% quoted by Whitridge Williams (1909) 45 years ago. Yet such figures tend to disguise the seriousness of pregnancy as an episode in the life of the diabetic. We have become accustomed to seeing these patients so cared for and their diabetic lives so organized that we fail to appreciate how closely they often come to disaster for themselves as well as their babies owing to the profound metabolic and endocrinal changes that accompany pregnancy. The hazards of repeated pregnancies in the diabetic in terms of morbidity are on the whole under-emphasized. Good control of diabetes throughout pregnancy can reduce the foetal mortality, as Lawrence and Oakley (1942) showed, but cannot abolish it.

Foetal mortality can be considered in relation to avoidable and unavoidable factors, the most important avoidable factor being control and supervision of maternal diabetes. But there are still unavoidable factors which make it impossible to reduce the foetal loss much below 20%. The last ten years have seen a

*Read in the Section of Obstetrics and Gynaecology at the Joint Annual Meeting of the British Medical Association, Canadian Medical Association, and Ontario Medical Association, Toronto, 1955.

considerable number of papers, each quoting from a relatively small series of cases, and each endeavouring to produce a lower foetal mortality than the other. These figures have, however, a limited comparative significance, if for no other reason than the lack of information given about the selection of cases and the indications for therapeutic termination. But they all emphasize a depressingly high foetal mortality—my own is 27% in the present series of 298 pregnancies. In marked contrast the 10% foetal loss quoted by Nelson, Gillespie, and White (1953) is a challenge to all those working in this field, and it is well known that they attribute their excellent results largely to hormone therapy. This subject is referred to again later.

The Pre-Diabetic State

It is now well established that married women who develop diabetes in middle life give obstetric histories very similar to those of the long-established diabetic. Peel and Oakley (1949) found a 23% foetal loss and a 27% incidence of babies weighing more than 10 lb. (4.5 kg.) in 237 pre-diabetic pregnancies, and other authors have quoted similar figures. There is, of course, very great theoretical significance in these facts, which suggest that the large babies and high foetal loss are not directly related to disordered carbohydrate metabolism of the established diabetic as such. It is thought that there may be a close relationship between the diabetogenic and growth factors of the anterior pituitary gland, and, further, that there is an overactivity of these for many years before the onset of clinical diabetes. It has been suggested that the pre-diabetic father may be a responsible agent in the production of giant babies, although it has not been possible to implicate him as a cause for high foetal loss.

This work has yet to be confirmed, but is mentioned because of its theoretical interest in relation to hereditary and genetic factors in these cases. The practical significance of these facts is simply that if we encounter pregnant women who give birth to very large babies of 10 lb. (4.5 kg.) and over or who have a series of obstetric disasters due to still-birth or early neonatal death, otherwise unexplained, it is important to investigate them as potential diabetics. A tendency towards adiposity may be noticeable and an abnormal glucose-tolerance curve discovered.

Diabetes Developing During or Shortly After Pregnancy

It is well known that pregnancy may affect carbohydrate metabolism. Apart from a lowered renal threshold which may account for the appearance of glycosuria, there may be a decrease in glucose tolerance. This may be due to the increased production of adrenal cortical hormones which occurs in pregnancy. The normal person's pancreatic islets are able to adapt rapidly to this increased mobilization of glucose, so that hyperglycaemia is only transient. In the patient with a diabetic diathesis, however, repeated pregnancies may put a severe strain upon the pancreatic islets, which then fail to adapt themselves. One may, on the one hand, encounter the patient who in succeeding pregnancies is suspected of diabetes because of persistent glycosuria and a glucose-tolerance curve which, while resembling the true diabetic curve, returns to normal as soon as pregnancy is over. On the other hand, a certain number of these patients do not in point of fact recover normal carbohydrate metabolism and become established diabetics requiring insulin as well as dietary control within a few months of delivery. Viewed from this aspect, pregnancy may be a precipitating factor in the development of clinically manifest diabetes. From the practical aspect of this problem it is essential to investigate persistent glycosuria in pregnancy not only during the pregnancy but for some time afterwards. It is equally important to follow up the patient who has delivered a large stillborn baby without other explanation and to investigate carefully the family history.

Pregnancy in the Established Diabetic

The problem presents itself most frequently in this way. The established diabetic seeks medical advice concerning the prospects of a successful pregnancy or she may be already pregnant. The literature is very sparse relating to the principles upon which either these patients should be encouraged to continue their pregnancy or therapeutic termination be advised. To give exact and rule-of-thumb indications for therapeutic termination is always difficult, if not impossible, for any pre-existing medical reason, and the same applies to the diabetic. But I am sure that if good results are to be obtained from the point of view of both the health and the well-being of the mother and of foetal survival a greater degree of selection is necessary than we have often carried out in the past. The following factors should be considered in every case.

1. *Family History.*—Whilst exact figures are still not available, no one would deny, on the clinical evidence we have, that a strong family history is obtainable in a large number of diabetic patients. What percentage of the babies born to diabetic mothers will ultimately become diabetic we do not yet know, and it will probably be another 25 years before we can have a sufficiently long-term follow-up of these babies to know the answer. But a strong family history of diabetes, especially if both father and mother are diabetics and have diabetic family histories, is a strong indication for not encouraging further reproduction.

2. *Vascular Complications of Diabetes.*—These are well known, and Nelson *et al.* divide their patients into six groups, of whom the last three—D, E, and F—show vascular complications of diabetes. From the viewpoint of foetal survival it is not possible to relate foetal loss directly with duration or severity of diabetes, but the presence of marked hypertension and albuminuria renders the prognosis very poor. As with hypertension and nephritis in the non-diabetic, an unexpectedly favourable outcome to a particular pregnancy may be achieved on occasion with careful management, but this does not alter the generally poor foetal prognosis in such cases. The increased hazards to the mother from superimposed toxaemia, accidental haemorrhage, retinitis, and renal failure are obvious.

3. *Obstetric History.*—There is no doubt that there exists an entity we sometimes call a bad obstetric history. It is often difficult to dissociate a bad obstetric history from bad luck and bad management, in this as in all bad obstetric histories. There is equally no doubt, however, that these recurrent obstetric disasters do tend to be repeated in the individual patient. We find that approximately 50% of our multiparous diabetics who lose their babies have already lost one or more in previous pregnancies. A recent obstetric disaster in a patient refusing termination illustrated the point. The patient, pregnant for the fifth time, with a mild hypertension, developed an acute toxaemic ante-partum haemorrhage at 34 weeks. Her previous four pregnancies had yielded two live and two dead babies. Such histories are not difficult to reproduce from our records. A further point of importance from this aspect of the subject is the tendency for congenital abnormalities of the babies to reproduce themselves in succeeding pregnancies.

4. *Availability of Expert Medical Care and the Co-operation of the Patient.*—There is little doubt that the most important factors concerned in the care of the pregnant diabetic patient are the availability of constant expert medical supervision and control of the diabetic condition throughout the pregnancy. An unintelligent and uncooperative patient may endanger not only the baby's life but also her own.

5. *Size of Family.*—Opinions may differ on this point, but the diabetic woman whose life is inevitably modified and limited to some extent by her disease is seldom a suitable person to have a large family, apart from the deleterious effects of repeated pregnancies upon her diabetic condition and the fact that the diabetic patient is not the most suitable for reproduction from the genetic standpoint. These considerations are debatable, however, and will not be further elaborated here.

A very careful assessment is therefore necessary at the beginning of pregnancy, and if good results are to be obtained the closest co-operation between a physician experienced in the management of diabetes as well as a good obstetric team is an essential. As an obstetrician I do not feel fully competent to deal with the detailed management of the patient from the point of view of dietary control and insulin requirements. I merely stress the difficulties that tend to arise from a lowered renal threshold, the

tendency to vomiting, and ketosis inherent in the pregnant state, which make the careful control of blood-sugar levels and diabetic state in general often very difficult. There is a tendency to instability, especially in the early weeks, if vomiting is present, and again about 20–24 weeks. It is surprising how often the baby survives repeated attacks of ketosis or hypoglycaemia; but the more frequent and severe they are the more must the foetal prognosis inevitably worsen. The requirements of insulin usually rise during pregnancy and fall during labour and the early puerperium. This latter is of special practical importance, because a continuation of the pregnancy level of insulin dosage after delivery may soon lead to dangerous hypoglycaemia unless the true condition is recognized and glucose, not insulin, given.

I now pass to aspects of the problem which are more particularly obstetric.

Effects of Diabetes on the Pregnancy

The effects during the first two trimesters of pregnancy are minimal. I know of no convincing evidence of an increased incidence of abortion in diabetics. They are particularly prone to pyelitis and to monilial vulvovaginitis. The latter, whilst being impossible to cure during pregnancy, can be kept under control by the usual methods of local treatment. I have found painting with gentian violet 1% and the daily use of "pruvagol" vaginal cream the most useful remedy. It is after the 28th week of pregnancy that the main obstetric complications arise—the rapid growth of the foetus, often associated with hydramnios, the development of pre-eclamptic toxaemia, and intrauterine foetal death. Cardell (1953) brought forward evidence to show that babies of less than 28 weeks gestational age are not larger than those of non-diabetic mothers. The factor, whatever it is, causing the giant baby is operative mainly in the last three months of pregnancy. The same applies to the development of hydramnios. Whilst we know that there is an excess of sugar in the amniotic fluid of the diabetic patient, there is no direct relation between the amniotic sugar level, the maternal or foetal blood-sugar levels, and the amount of liquor amnii (Peel and Oakley, 1949).

Pedersen and Jorgensen (1954) have shown a higher incidence of hydramnios and a greater amount of fluid in a series of cases treated for only a short time compared with a series treated throughout their pregnancies and hospitalized during the 30 days before delivery. They were, however, unable to deduce which part of the treatment given was the effective agent in reducing the incidence of hydramnios. Personally I have found no method of control of the development of hydramnios of any value, and abdominal paracentesis as a measure for reducing the fluid temporarily is also of very doubtful value. In my experience it is apt to cause intrauterine death within a few days, however slowly the liquor is withdrawn. Pedersen and Jorgensen's treatment did not include hormones, mercurial diuretics, and ammonium chloride, all of which are used by Nelson *et al.* (1953) and given pride of place as therapeutic agents used to decrease the incidence of all the obstetric complications in the last three months of pregnancy. The incidence of pre-eclamptic toxaemia is higher than in non-diabetic pregnancies, but the factual incidence varies with the extent to which premature termination is practised.

The incidence of toxaemia in the present series is 13%, but figures varying from 3 to 50% have been quoted. The development of both or either of these complications (and there is an undoubted association between the two) is an event of supreme importance. From the foetal point of view the development of marked hydramnios is more serious than toxaemia, because it so often heralds intrauterine foetal death.

Much has been written about the factors responsible for the high foetal loss in diabetic pregnancy, and some of the possible factors are briefly mentioned:

1. *Severity of Diabetes.*—There is no relation between the severity of diabetes, as judged by insulin needs, and foetal loss.

2. *Age of Onset of Diabetes.*—Oakley (1953) has shown that there is no relation between foetal loss and age of onset of diabetes (Table I).

TABLE I.—*Relation of Foetal Mortality to Age of Onset of Maternal Diabetes (Oakley, 1953)*

Age of Onset of Diabetes	No. of Babies	Foetal Mortality
1–15	70	21 (30%)
16–24	105	24 (23%)
25 and over ..	92	29 (31%)

3. *Duration of Diabetes.*—Oakley has also shown that there is no relation between foetal loss and duration of diabetes (Table II).

TABLE II.—*Relation of Foetal Mortality to Duration of Maternal Diabetes (Oakley, 1953)*

Duration	Cases	Stillbirths	Neonatal Deaths	Total
0–4 years ..	97	19	10	29 (30%)
5–9 ,, ..	72	9	11	20 (28%)
10–14 ,, ..	55	4	10	14 (25%)
15–19 ,, ..	28	4	2	6 (21%)
20+ ,, ..	11	0	3	3 (27%)

4. *Toxaemia.*—The foetal loss in toxaemic cases in the present series is 44%—definitely higher than in the non-toxaemic cases.

5. *Hydramnios.*—It is almost impossible to obtain the exact incidence of this from the literature and, indeed, from my own cases. Some excess liquor is present in nearly all diabetic patients, so that it is most difficult to decide what constitutes hydramnios. Its development fairly acutely between 30 and 36 weeks is always, in my experience, a bad prognostic sign and indicates the need for early termination.

The exact and immediate cause of intrauterine death has not yet been determined. Its incidence steadily rises as the pregnancy advances towards term (Peel and Oakley, 1949), owing presumably to placental insufficiency. One imagines the rapidly growing and pathologically large baby outgrowing the supply of oxygen which can reach it through the placenta. There are two pieces of evidence which suggest the explanation of intrauterine death, and at present we are carrying out investigations along these lines. During the course of a prolonged clinical trial of hormone therapy, an extensive series of hormone assays has been carried out by Professor C. H. Gray at King's College Hospital. The results of these assays have been subjected to critical and statistical analysis and will be published in due course. The results so far suggest that if perinatal death is impending an abrupt and progressive drop in the excretion of pregnanediol and allied chemical compounds in the urine occurs between the 30th and 32nd weeks of pregnancy. This is presumably an indication of failing placental function, but it suggests the possible value of urinary pregnanediol estimations from the prognostic point of view even though the biochemists are not yet completely satisfied with the specific method of estimating this substance or its precise relation to progesterone metabolism.

We are at present carrying out this test weekly from the 28th week onwards, and look upon a progressively falling excretion after the 32nd week as evidence of impending intrauterine death. The number of cases on which we have so far carried out this investigation is not yet large enough to enable us to draw a firm conclusion of its value. Another investigation at present being carried out in our department is an estimation of the cord haemoglobin of the baby at birth and also the oxygen saturation in the blood. The work of Walker (1954) in relation to the post-mature foetus has shown that the baby compensates for a falling oxygen saturation due to placental insufficiency by a steady increase in the haemoglobin level, and that therefore the foetal haemoglobin level steadily increases up to the time of delivery. We are finding haemoglobin levels in the diabetic

babies delivered at 36 weeks as high as we would expect at term, but again I cannot yet draw final conclusions until we have a sufficiently large series.

White's claim that hormone therapy minimizes the overall foetal loss has been doubted by many authors in Great Britain. The Medical Research Council has organized a clinical trial of hormone therapy, employing both stilboestrol and ethisterone in doses shown in Table III.

TABLE III.—*Schedule of Daily Hormone Dosage*

Stage of Pregnancy	Stilboestrol (mg.)	Ethisterone (mg.)
Up to the end of the 19th week..	50	25
20th–23rd weeks inclusive ..	100	50
24th–27th " " ...	100	75
28th–31st " " ..	150	125
32nd week until delivery ..	200	250

We ourselves have treated 56 patients with hormones according to this schedule: 35 babies survived, 21 were lost. Compared with a control series there was no alteration in the incidence of oedema, albuminuria, toxaemia, or hydramnios, and no difference in the birth weights. The more comprehensive figures from the Medical Research Council include eight other centres besides our own. They bear out our own findings and are in process of publication.

It appears from our investigations that, although hormone therapy has no effect upon foetal survival, it does affect the level of hormone excretion. It does not, however, prevent the drop in the excretion of pregnanediol and allied chemical compounds in the urine that occurs after the 32nd week in cases where foetal death is impending. This is really what one would expect on theoretical grounds. The altered hormone balance is the result of failing placental function and not the cause of it. Substitution therapy apparently corrects the hormone imbalance as judged by excretion studies, but has no influence upon the physiological function of the placenta and so has no effect whatsoever upon foetal survival.

Mode and Time of Delivery

If pregnancy is allowed to continue to term intrauterine death may occur. Some clinicians allow pregnancy to continue until the onset of spontaneous labour, in the belief that premature termination, whilst preventing intrauterine death, does not lower the overall foetal loss, because of an increased incidence of neonatal death due to prematurity. I have always favoured premature termination, however, in spite of a high incidence of neonatal death. Other factors than prematurity come into the causation of neonatal death, and we hope for a steady improvement in foetal survival, whereas at present there is little that we can do to prevent intrauterine death. For some years, whilst the hormone therapy trial was being conducted, we decided to standardize obstetric management as much as possible. In consequence we carried out caesarean section at the 37th week in all primiparae and in a great many multiparae. Until antenatal treatment can effectively lower the incidence of intrauterine death and foetal size, caesarean section must inevitably remain the most suitable method of termination. Following artificial rupture of the membranes, there is often a long interval before the onset of labour, especially in the primipara, and this may be followed by inertia in the first stage. During all this time difficulties may arise in controlling the diabetic condition of the mother, with the result that foetal distress may occur. Therefore even after induction caesarean section may become necessary. Nevertheless I think one should exercise judgment about the best method of termination. In the presence of hydramnios, toxaemia, a very large baby, or a very unfavourable cervix, caesarean section is, I think, best, especially if termination is necessary before 36 weeks. On the other hand, in multiparae with a satisfactory previous obstetric history and in some primiparae, where the baby is not unduly large, where hydramnios is minimal and the cervix favourable, induction should be employed, especially if it has been thought safe to allow the pregnancy to proceed to the 38th week. It has always been my experience that neonatal death was lower in cases delivered vaginally. Our neonatal death rate is 18.5% in 199 caesarean sections. Our induction number is small by comparison, but out of 39 patients induced (the baby being alive at the time of induction) 9 babies were lost, but 4 of these died during labour, so that the neonatal death rate was 12%. These figures are not of statistical significance, but they suggest, at any rate, that mode of delivery has little to do with neonatal death. Against induction are, of course, the hazards of a long labour and the difficulties in the vaginal delivery of a very large baby. Very careful judgment is necessary, therefore, in selecting cases suitable for induction.

The majority of babies that die in the neonatal period die within 48 hours of birth. The incidence of congenital abnormalities in our series is 8%, but Cardell has shown that their incidence in post-mortem material is not higher than normal, indicating that congenital abnormalities are not an important cause of neonatal death. Equally I have shown that hypoglycaemia is not an important cause. We have found, however, that in 85% of our babies dying in the neonatal period hyaline membrane disease is demonstrable. Space does not permit further discussion upon this interesting condition, which is known to occur predominantly but by no means exclusively in premature babies delivered by caesarean section, but it indicates the main lines upon which the newborn baby must be treated. Reutter (1954) suggests that intrauterine anoxia may be a predisposing factor in the subsequent development of hyaline membrane after birth. This would certainly lend support to the conception that the very babies that die in the neonatal period are the ones that would have died *in utero* from anoxia had they not been delivered.

Again space does not permit of a detailed discussion concerning the management of the newborn of the diabetic mother. Suffice it to say that the first 24 hours are the most critical; the maintenance of a good airway and gastric suction are vital; the administration of oxygen is invaluable; also, the nurse must be experienced in the care of the premature baby. I have little experience yet of the value of corticotrophin (A.C.T.H.) and cortisone or the administration of potassium to the baby. There are theoretical considerations suggestive of the possible value of this, and preliminary investigations are being undertaken in my department. In this subject there is a rich field for speculation and research, and I have been able merely to touch on the main problems involved and indicate the lines upon which we have been working and upon which we intend to proceed.

Summary

The clinical association of diabetes mellitus and pregnancy is still comparatively uncommon, though increasing. The obstetrical interest lies in relation to problems of foetal size, placental function, intrauterine and neonatal death, hydramnios, toxaemia, and congenital foetal abnormalities in general.

The overall foetal mortality remains high.

Three groups are briefly discussed: (*a*) the prediabetic; (*b*) diabetes developing during or soon after pregnancy; (*c*) pregnancy in the established diabetic.

The indications for therapeutic termination are considered.

The main problems during the antenatal period arise during the last trimester, when there is an especial tendency for the development of hydramnios and toxaemia, and for intrauterine death to occur.

The high foetal loss is considered in relation to severity, age of onset, and duration of diabetes, and to hydramnios and toxaemia.

The results of a clinical trial using oral hormones (stilboestrol and ethisterone) are given, suggesting that they have no effect upon foetal survival.

Brief reference is given to hormone assays which have been carried out at King's College Hospital, and their possible prognostic significance indicated.

Premature termination of pregnancy before the end of the 37th week is recommended, and the relative places of caesarean section and induction of labour are discussed.

The importance of hyaline membrane disease as a cause of neonatal death and its possible relation to intrauterine anoxia are explained.

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CLINICAL ASPECTS OF ATYPICAL CORONARY DISEASE*

BY

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It is generally agreed that more cases of coronary arterial disease are being recognized to-day than formerly. We know from Ryle and Russell (1949) that in Great Britain there has been an increase in the mortality from coronary disease in the post-war years, but the increase is less rapid than in the pre-war years. This increased mortality has occurred in spite of improved methods of treatment by anticoagulants, etc. Early and accurate diagnosis is therefore of fundamental importance, in order that the treatment can be started as soon as possible.

I propose to deal with atypical angina pectoris and with some of the clinical aspects of cardiac infarction.

Angina Pectoris

First let us remember that it was William Heberden who was the first to give, in 1768, a clear and accurate description of angina in a paper entitled, "Some Account of a Disorder of the Breast." In this paper Heberden showed that angina pectoris may occur with no physical signs and with an apparently normal cardiovascular system, and this has been recognized ever since his time. A diagnosis often has to be made on the history obtained from a patient.

The familiar picture of angina pectoris is that of pain in the centre of the chest radiating down into the left arm to the wrist. It is less well known, however, that the pain may radiate in other directions, or the case may present itself with different symptoms. In a series of cases investigated by me during a five-year period, pain extended from the chest into both arms in 17% of the cases.

In the "reversed" type the pain in all respects follows the classical pattern of angina pectoris, except for the distribution and radiation, which is the reverse of the usual. The patient complains that the pain starts in his left hand, wrist, or arm, or the left side of his neck, and radiates up into his chest, and is associated with the usual feeling of constriction in the chest.

Next, there is the patient who complains of a sensation of a band round his wrists or arms. On careful inquiry he may admit that it sometimes amounts to a pain; he may not mention, unless asked, that it is directly related to exertion or is accompanied by a retrosternal pain. He may even have been treated as a case of neuritis or myofibrositis before a cardiac cause for his symptoms was suspected.

Quite a number of my cases have complained of a pain in the jaws or gums. One man said that he could not wear his dentures after a meal because of this pain; another man said that his jaws "ache at times."

It will be remembered that the word "angina" does not mean pain, but a strangling. There are the patients whose main concern is the choking or strangling sensation in the throat. An interesting example of this was a patient who reported to my out-patient clinic two years ago, and gave a history of a curious choking sensation in his neck, saying that he felt he was "breathing in cold air." This had been present for two months, and occurred only on walking; it had not interfered with his work, but he had noticed a pain across his chest, with slight dyspnoea, on exertion. At that time a diagnosis of atypical angina had been made. Two years later he gave a classical history of angina with considerable incapacity.

Several examples of angina have been sent to my clinic by doctors because they have been worried by the patient's complaint that the pain is worse after meals and they suspected some form of dyspepsia. A recent example of this was a carpenter, who found that his capacity for work was curtailed by his midday meal; he stated that he could do four times as much work in the afternoon if he went without his lunch. A full and carefully taken history revealed that this limitation of work was due to angina, which followed on slight exertion after a heavy meal.

The details of another patient, who experienced pain in his phantom hand, are of special interest. Two such cases have also been recorded by Sir Henry Cohen and Wallace Jones (1943). The man, aged 58, had had a gunshot wound of his left elbow in the 1914–18 war. After excision of the joint, sinuses and sequestra developed, so that amputation above the elbow had to be performed. Three months after the operation angina of effort developed; the patient complained that the pain radiated into the elbow and all the fingers of his phantom hand. When, six months later, he had an attack of coronary thrombosis, the pain followed a similar distribution in the phantom hand.

If young patients develop angina without any obvious cardiovascular disease the possibility of hypercholesterolaemia may be considered, although it is a very rare condition. I have recently seen two members of one family in which this interesting rarity existed. A Cypriot waiter, aged 24, attended my clinic complaining of severe angina pectoris of three months' duration. Since the age of 12 he had had yellow nodules in the skin (xanthomata). An electrocardiogram was normal, but after an exercise test it showed the classical E.C.G. changes of angina (depressed ST segments, etc.). His blood cholesterol was 650 mg. per 100 ml. His angina was considered to be due to deposits of cholesterol in his coronary arteries, and to be part of the general disease known as xanthomatosis tuberosum multiplex. He died two years later of cardiac infarction. His sister, aged 30, came to my clinic about this time; she had had skin nodules for eight years and angina pectoris for three years. Her blood cholesterol was 860 mg. per 100 ml. She died suddenly about one year later, whilst out shopping, as a result of coronary thrombosis.

These are some of the unusual types of angina. How, then, can we make a diagnosis in an atypical case? The answer is simple; it is by a most scrupulously taken history. Firstly, the method in which the patient gives his history is of great value; his whole manner of presentation is convincing, since he has no need to use the florid and exaggerated phrases that are so often associated with patients suffering from the neuroses. The patient is usually intelligent, and gives a definite history, showing how handicapped he now is, whereas previously he was a fit man. Moreover, there is an absence of inconsistencies in his history; there may be variations in the amount of exciting exercise, but

*Read in the Section of Medicine at the Joint Annual Meeting of the British Medical Association, Canadian Medical Association, and Ontario Medical Association, Toronto, 1955.

the whole story rings true from beginning to end, and fits into a clear pattern of a man limited by his disability, for reasons which he does not understand. Secondly, the symptom (pain, discomfort, or constriction) is related to exercise and to a definite degree of exercise, and also to emotion; it is, in addition, influenced by heavy meals and a cold wind, each of which limits his capacity for exertion. Finally, the symptoms are almost always associated with a central chest pain, accompanied by a constriction in the chest, but this may well be overshadowed by the patient's concentration on a symptom in another situation, for which he presents himself.

Myocardial Infarction

Two aspects only of the problem of diagnosis of myocardial infarction are here dealt with. Firstly, are there any warnings of an attack of cardiac infarction, and, if so, what are they? The second aspect concerns the unusual manifestations of cardiac infarction—particularly the patient complaining of abdominal pain, and also the patient with the so-called silent or painless infarct.

Whereas the classical picture of cardiac infarction due to coronary thrombosis is the sudden onset of severe pain with shock and collapse, followed frequently by congestive heart failure, it is becoming increasingly recognized that certain warning symptoms may occur, which, if suitably treated, may result in the prevention or postponement of actual infarction of the myocardium.

Prodromal Symptoms Including "Indigestion"

The fullest and most recent study of the subject of premonitory pain was carried out by Mounsey (1951) at the British Postgraduate Medical School, Hammersmith. He came to the conclusion that it occurred often enough to form a recognizable clinical group.

I have made a careful study of my records of all patients seen for the first time during a recent five-year period, in whom a diagnosis of coronary thrombosis had been made; in particular, I have investigated any history of early symptoms or special features. These patients have either been under my care at University College Hospital as in-patients or have been seen in private practice. I have limited the investigation to in-patients and private cases because the notes of such patients are much fuller and more accurate than those of out-patients. Those patients who were so ill on admission to hospital that they were unable to give a complete history have not been included in the series. Three criteria have been used in the investigation: (1) the diagnosis of cardiac infarction must be clear, with a typical E.C.G., or confirmed at necropsy; (2) there must be clear evidence of the time at which the cardiac infarction took place; and (3) a good history of the events *before* the infarction occurred must have been obtained.

There were 23 cases out of 75 in the series with premonitory symptoms—that is, 30%. I have studied the details of the histories of these 23 patients to see if they can be grouped together in any way, and I feel that they might be put into the following three groups: (1) Angina of effort, of recent onset, or increasing in severity recently. (2) Constant sternal pain, roughly simulating angina in its site and radiation. (3) Attacks of sternal pain, quite unrelated to exertion, emotion, etc.

In the first group (angina of effort) sometimes the angina of effort is of recent onset; in others there has been a long history, but recently the incapacity has been progressively increasing over the last one to three months. This group consisted of five patients, of whom three died—a mortality of 60%, the highest.

In the second group (constant sternal pain) this symptom occurred up to three weeks, with an average of six days, before the onset of the coronary thrombosis. Radiation of the retrosternal pain occurred in all except one case; none had previously had angina of effort. There were six patients in this group and no deaths.

In the third group (attacks of sternal pain not related to effort or emotion) this symptom varied in duration between one day and one month, with an average of two weeks. The attacks were usually frequent and short-lasting. About one-quarter of the patients had previously had angina of effort, and these knew that this prodromal pain was a different one. Of the eleven patients in this group two died. There were also four patients who complained of excessive tiredness or feeling seriously ill prior to the onset of the attack of cardiac infarction.

I would like to refer here to the term "indigestion," which is in my experience not infrequently used by the patient, and sometimes by the doctor. It occurred in one-third of my patients' histories, and these cases have been included in groups 2 and 3. It is so easy for a patient, and even for a doctor, to attribute an upper abdominal or retrosternal pain to indigestion, especially if it is worse after meals or is associated with wind. Care must therefore be taken by a doctor in making such a vague diagnosis as "indigestion," or in accepting the patient's own label, in cases of hypertension, angina pectoris, etc., and in persons possibly liable to coronary occlusion. Perhaps this aspect might be illustrated by the history of a patient, a medical practitioner, who consulted me three days after he had had his premonitory attack: this consisted of pain which he attributed to an injudicious meal taken late at night. In the absence of signs of cardiovascular disease and on the strength of a normal electrocardiogram (and unfortunately ignoring the importance of a phrase used by him—namely, a "severe vice-like pain") I labelled it "flatulent dyspepsia." Six days later I was called out to see him in a typical attack of cardiac infarction, with classical E.C.G. changes; he recovered well and is now back at work.

The difficulties of recognition of these prodromal symptoms and of their significance is in no way underestimated. That they do occur in a fairly high percentage of cases of cardiac infarction (30% in this series) is generally agreed, but to recognize them *before* an attack of infarction may be almost impossible.

The mortality of patients with premonitory symptoms has been shown in all published series to be lower than the general average mortality, though there is insufficient evidence at the moment why this should be so. As regards the immediate mortality rate in the series with adequate histories recorded here, 20 of the 75 died (27%). Out of the 52 patients without any history of warning pain, 15 died (30%); whereas only 5 out of the 23 with premonitory symptoms died (22%).

It is important for us to look out for the cases with prodromata amongst our patients, and if we do we shall perhaps recognize them more frequently. It is well worth while in known cases of hypertension and of angina to arrange for a regular annual review of their condition, with detailed inquiries into any new symptoms; but care must be taken not to alarm the patient unduly.

Unusual Clinical Pictures

The two clinical pictures of cardiac infarction which are of greatest interest and most apt to lead to pitfalls in diagnosis are those presenting as an acute abdominal emergency and those cases in which pain is not a prominent symptom in the patient's history—that is, the so-called silent or painless infarct.

A case of coronary thrombosis presenting as an acute abdominal emergency calls for consultation and close co-operation between general practitioner, surgeon, and physician, because this condition may simulate, for example, a perforated duodenal ulcer or gall-stones. Some years ago I saw a surgeon who during the previous three days had had severe upper abdominal pain. Being a surgeon, he diagnosed his own case as "gall-bladder disease" or "partial volvulus." On account of this diagnosis that he had made he continued to do his full hospital work, including operations, until a few hours before he collapsed. When

seen by me he showed the clinical picture and E.C.G. changes of coronary thrombosis, from which he died two days later.

Help towards a correct diagnosis of myocardial infarction may be obtained by considering the age and sex of the patient, and the presence of any predisposing factor, such as hypertension, angina, etc. Conversely, a history of peptic ulceration or long-standing flatulence would point towards an abdominal cause for the pain. Whilst the abdominal pain may be so severe that it attracts the patient's attention as the major symptom, there is always, in my opinion and experience, some retrosternal pain, and this is a constant pain, never spasmodic or colicky; it is a valuable diagnostic feature of infarction. In abdominal infections a raised temperature would be expected, whereas in cardiac infarction fever is low and seldom occurs until some days after the onset. Breathlessness and cyanosis are less often seen in abdominal catastrophes than in cardiac lesions. In a large number of cases the immediate electrocardiogram will give diagnostic evidence of infarction, though the E.C.G. may have to be repeated two or three days later to be certain to exclude infarction.

My former chief, the late Sir Thomas Lewis (1933), wrote that "pain is not invariable" in coronary thrombosis. While this may be so in cases of sudden death from myocardial infarction, since no one can deny or confirm such an opinion, it is, in my experience, rare to find that a patient who has had an infarct has had no pain. In other words, a silent or painless myocardial infarct is exceptional.

What are some of the ways in which such patients may present themselves, and why is the attack often thought to be painless when actual pain frequently does occur? Some clinical conditions which should arouse our suspicions will now be considered.

Firstly, sudden onset of congestive heart failure occurring in a middle-aged person, especially if there is no immediate exciting cause, such as physical overwork or an infection, and where there is no obvious underlying disease, such as mitral stenosis or hypertension. Also, congestive failure without cardiac enlargement, in the absence of hypertension, is suggestive of coronary thrombosis in the appropriate age groups. Secondly, acute pulmonary oedema and left ventricular failure, especially with falling blood-pressure readings. Thirdly, unexplained irregularities of rhythm, such as heart-block and auricular fibrillation, etc. Fourthly, other signs of a failing heart, such as gallop rhythm, pulsus alternans, and Cheyne–Stokes's respiration.

The above four groups are examples of the type of case in which careful and full investigation may reveal that myocardial infarction is the underlying cause. Success in diagnosis often lies in remembering the possibility of coronary occlusion as a cause, and in watching for E.C.G. changes and late signs and complications.

While pain is almost invariably present at some time during the episode of myocardial infarction, it is often forgotten by the patient. This, I find, is often due to the fact that some other symptom predominates in the patient's memory. Usually it is dyspnoea; sometimes it is that he feels extremely ill; at other times he attributes the pain to wind or indigestion. It will be seen, therefore, that the attack may be labelled painless because the patient has omitted to mention the pain. The onus of eliciting a history falls on the doctor, and, as it may be difficult to obtain the story of the pain, it is necessary, in my opinion, to carry out an unhurried, careful, and thorough interrogation of the patient when he is fit enough; the value of such cannot be overestimated. Such questions as, Have you ever had any wind or indigestion? or, Why exactly did you or your relatives send for the doctor? will not infrequently bring out a story of pain, which had previously not been mentioned. It is well worth while trying to obtain experience in such history-taking without asking leading questions, and the time and trouble spent on getting such a history will be amply rewarded.

A recent example may be quoted to illustrate this difficulty. A works foreman, aged 46, consulted me for chronic bronchitis of six years' duration and increasing shortness of breath. The latter symptom had troubled him for only one month, limiting his activities to walking 200 yards on the level and preventing him from doing his job as foreman. On examination his dyspnoea appeared to be out of proportion to the degree of emphysema, and was attributed by me to a failing heart. Suspecting cor pulmonale as the cause, I took an E.C.G., and was somewhat surprised to find that it showed the classical changes of a recent posterior cardiac infarct. On inquiry about discomfort or pain in the chest, he then described the pain typical of ischaemic heart disease, which he had noticed during the last month or so. He had not mentioned it previously, as he thought it was tightness due to his bronchitis and his dyspnoea.

If we wish to look out for the atypical clinical pictures and for the prodromata of myocardial infarction, is there any guide to help us to recognize who are susceptible subjects? There are several classes of persons who are unduly vulnerable. They can be classified into three groups: (1) Those men over the age of 45 who have a family history of coronary disease or hypertension or who are found to have abnormal electrocardiograms. (2) Patients with certain diseases—for example, high blood pressure, diabetes mellitus, angina of effort; those who have already had one attack of cardiac infarction, etc. (3) Those in certain occupations, such as those shown by Ryle and Russell to have a high mortality—for example, physicians and surgeons; proprietors of wholesale businesses, judges, barristers, and solicitors. These are occupations requiring a high degree of mental activity, and also considerable anxiety and stress in their performance.

If, therefore, in these vulnerable subjects we look more carefully for the prodromal group of symptoms, and for variations in the classical clinical picture of coronary disease, we may achieve a greater accuracy in diagnosis and, with the aid of modern anticoagulant and other methods of treatment, help to lower the mortality of this serious disease. Finally, a word of warning must be given about the risk of causing undue alarm to a nervous or otherwise healthy person, and turning him into a cardiac invalid. We have to steer between the Scylla of missed diagnosis on the one hand and the Charybdis of the risk of producing cardiac invalidism or neurosis on the other.

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"If the telephone rings between 11.30 p.m. and 8 a.m. the chances are even that the physician will encounter a parturient woman, a corpse, or a sufferer from biliary-tract disease, respiratory infection, or injury," writes W. W. Forbes in an article in the *New England Journal of Medicine*, July 14, 1955, analysing 200 consecutive night calls in a Massachusetts "family type" practice. In 65 cases the complaints were those attendant on birth or death, and of the remaining 135, 48 were of non-traumatic pain and 23 of injury. 16 were paediatric calls, an unexpectedly low number, and 10 of these had upper respiratory infections. Adequate diagnosis was made in all but 2 cases, which proved to be hysteria presenting as backache, and cholecystitis. The telephoned description of the symptoms proved a reliable clue to diagnosis, though the degree of illness was largely exaggerated. Definitive therapy was carried out in 172 of the 185 living patients: sedatives were given to 40% of the cases, antibiotics to 6%, and minor surgery to 14%. The author reports that 22 of the calls were unnecessary, 21 should have sought earlier or later help, and 3 should have been handled by a dentist.

TREATMENT OF OESOPHAGEAL VARICES IN PORTAL HYPERTENSION BY MEANS OF SCLEROSING INJECTIONS*

BY

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In 1949 I briefly described a method of treating oesophageal varices by sclerosing injections based upon nine cases (Macbeth, 1951). The purpose of the present communication is to describe further experience with the method in a total series of 30 cases, and to attempt to justify its use as a valuable means of treatment in patients suffering from portal hypertension.

Portal Hypertension

This term, coined by McMichael in 1932, is descriptive of an increase of pressure within the portal venous system. It may be intrinsic by reason of fibrosis of the liver, or extrinsic because of thrombosis of the portal vein or of one of its main tributaries.

The portal system anastomoses with systemic veins at a number of points, but the lower end of the oesophagus and the cardiac end of the stomach provide a site where back-pressure from the portal side is peculiarly apt to produce varicose dilatations.

Bellis (1942) compared the portal venous pressure with that in an ankle vein in 16 human subjects who showed no evidence of portal obstruction. He found that the portal pressure ranged from 14 to 22 cm. of saline, while that at the ankle was 5 to 12 cm. Where valves are present in the veins such a pressure differential would not be expected to cause any dilatation of the systemic veins of the oesophagus. Whipple (1949) states that the normal portal pressure is 6 to 14 cm. of saline, but that in hypertension is 40 to 60 cm. Where the pressure is so markedly raised on the portal side any valves present in anastomotic veins would soon become incompetent, the blood flow would be from both ends, and varicosities would develop. Gradually further valves would give way, and ultimately the blood would find its way into the main systemic veins draining the oesophagus.

Anatomy

A comprehensive description of the veins of the oesophagus has been given by Butler (1951). He classified the veins as (*a*) intrinsic, which include subepithelial, submucous, and perforating; (*b*) extrinsic (or subserous), which are formed by the union of groups of perforating veins; and (*c*) venae comitantes of the vagal nerves, which run longitudinally in the adventitia of the oesophagus.

The subepithelial intrinsic veins are present throughout the oesophagus, and are continuous with those of the stomach. They drain without the intervention of valves into the submucous group. The submucous veins lie beneath the muscularis mucosae throughout its length. In the neck they drain via the perforating veins into the internal jugular vein; in the thorax similarly into the azygos veins; at the lower end they increase in size, become tortuous, and descend to join those of the stomach. Valves are inconstantly present at the level of the cardia. The perforating veins traverse the muscular coats and join the extrinsic veins. At this point of junction they are guarded by valves which direct the blood outwards.

The venae comitantes of the vagal nerves run longitudinally and link the left gastric vein directly or indirectly with the azygos system.

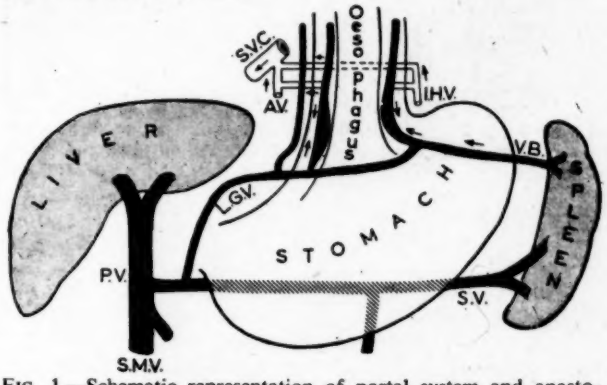

FIG. 1.—Schematic representation of portal system and anastomosis at oesophago-gastric junction (adapted from Learmonth). P.V.=Portal vein. S.M.V=Superior mesenteric vein. L.G.V.=Left gastric vein. A.V.=Azygos vein. S.V.C.=Superior vena cava. I.H.V.=Inferior hemiazygos vein. V.B.=Vasa brevia. S.V.=Splenic vein.

The extrinsic veins drain into the systemic veins except in the abdomen, where three or four join the left gastric vein.

There are, therefore, three routes in this area whereby portal blood may reach systemic veins.

Butler states that any or all of the veins of the oesophagus may become varicose in cases of portal obstruction, and this is borne out by the examination of necropsy specimens.

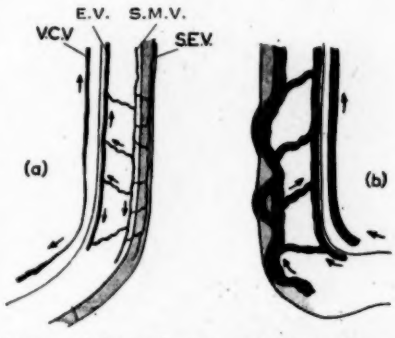

FIG. 2.—Schematic representation to show dilatation of veins. (*a*) Normal. (*b*) Abnormal. V.C.V.=Vena comitans of vagus. E.V.=Extrinsic vein. S.M.V.=Submucous vein. S.E.V.=Subepithelial vein.

The submucous veins of the stomach may also become varicose, but Learmonth (1951) states that this occurs later than in the oesophagus, and this observation fits in well with the clinical finding that gastric bleeding is rarer than oesophageal. The dangerous subepithelial varices of the oesophagus may develop by reason of the back-flow of blood coming into them indirectly via their own submucous veins, or because (as Learmonth says) the muscularis mucosae disappears by atrophy over submucous varices (Figs. 1 and 2).

Pathological Evidence

A mounted specimen of oesophagus taken from a patient who died of liver disease is shown in Fig. 3.

Sections of oesophagi have been specially prepared after injection of the portal veins of a recently dead infant and a similar young adult, following the method suggested by Butler (Figs. 4 and 5). The distribution of the veins as described by him is amply confirmed.

Further sections have been made of the oesophagi of patients who had died of liver failure, and in whom injection of varices had been carried out during life. In these it can readily be seen that the dilated varices impinging upon the lumen are in reality submucous veins over which the muscularis mucosae has disappeared (Fig. 6), as Learmonth

*Read in the Section of Otolaryngology at the Joint Annual Meeting of the British Medical Association, Canadian Medical Association, and Ontario Medical Association, Toronto, 1955.

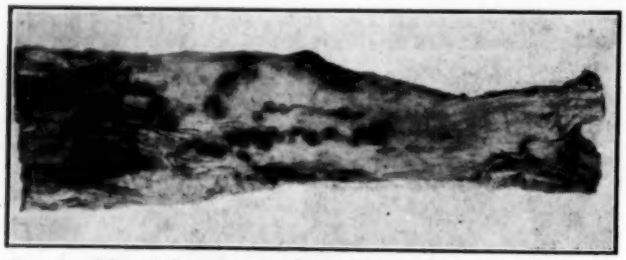

Fig. 3.—Mounted specimen of oesophagus from a patient who died of liver failure, showing injected and thrombosed veins, and one vein whose rupture was the cause of accompanying fatal haemorrhage.

(1951) suggests. Also there can be seen veins whose lumen has completely disappeared and been replaced with fibrous tissue (Fig. 7).

Methods of Treatment

It is obvious that methods of treatment must be aimed solely at relief of the varices from which these patients may bleed, since the underlying cause of the portal hypertension, whether intrinsic or extrinsic, is incurable anyway.

In many cases haematemesis is the only symptom of which the patients complain. Any method which results in control of the varices may prolong life in those patients with liver damage, and may give lasting relief to those without. The following methods have been used:

Fig. 4.—Oesophagus of child aged 3 months, congested but otherwise normal, full thickness. Showing subepithelial, submucosal, perforating, and adventitial (near vagus) veins.

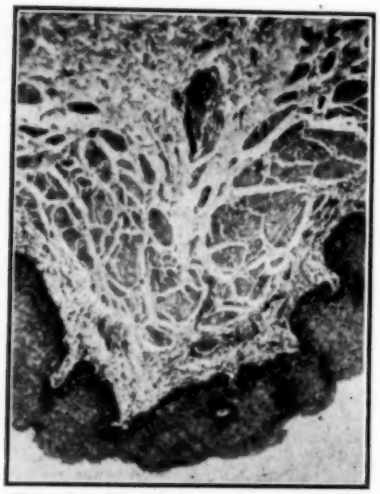

Fig. 5.—Oesophagus of young man (killed in road accident), inner half. Showing normal appearance of veins with much thicker adult epithelium and muscularis mucosae.

1. *Splenectomy* has been credited with diminishing the blood supply to the portal veins by 20–40% (Pemberton, 1931; Adams, 1951). This results in a temporary decrease in the portal pressure, but the pressure soon rises and varices may recur and bleed after an interval of freedom from trouble. Learmonth (1951) recommends splenectomy as preventing external anastomoses in relation with the swollen spleen.

2. *Ligature* of the short gastric, coronary, and diaphragmatic veins has proved useless because other venous channels open up.

3. *Gastric transection* aims at interrupting the veins in the walls of the abdominal oesophagus near the cardia. An encircling incision is made down to the mucosa, all veins are ligated, and the incision is then sewn up. This is not a minor procedure and is attended by a significant mortality rate. Other surgeons use a similar encircling incision of the oesophagus. These operations belong essentially to the same category as subdiaphragmatic venous ligature, and suffer from the same likelihood that new venous channels may open up. I have been told of one patient who developed a sudden intractable ascites after this type of operation; and of another who developed peritonitis, possibly because ascitic fluid became infected. Both died.

4. *Total gastrectomy* is an even more heroic procedure belonging to the same group.

5. *Porto-caval venous anastomosis* would appear to be the most logical method of relieving portal hypertension by a direct transfer of blood from the one system to the other. Blakemore (1951) reported 111 cases up to May, 1950, with a 16.2% mortality due to the operation. He states that "the operative risk is inversely proportional to the normality of the liver," and therefore it has its greatest application in extrinsic cases. In successful cases it seems undoubted that varices become smaller or disappear. Unfortunately the operation is technically difficult and thrombi may form at the anastomotic site.

Fig. 6.—Dilated submucosal veins breaking through muscularis mucosae, which appears atrophic over them. Subepithelial veins not very large.

Fig. 7.—Old thrombosed submucosal vein close beside new varix.

6. *Sclerosing injections* have been carried out since Crafoord and Frenckner (1939) reported a successful case. Success with the method has not been uniform, but those who have tried it and given it up may either have used unsuitable techniques or have encountered hopeless cases, and in consequence have failed to persevere. The most recently published series was that of 20 cases by Kempe and Koch (1954). They stress the value of splenectomy as a preliminary procedure. The present series of 30 cases has been treated by injection in the last 12 years in the department of otolaryngology at the Radcliffe Infirmary.

Material

Two main groups of patients have been recognized—those with and those without liver damage. Of the 30 cases, 14 have been classified as belonging to the former category and 16 to the latter. On occasions it may be difficult to give a hard-and-fast opinion on this point without a liver biopsy, but the biochemical liver-function tests will usually give reasonably accurate information. Almost invariably a severe haematemesis requiring emergency treatment is the event which leads to the diagnosis of portal hypertension.

G. J. Fraenkel (1955, personal communication) has made a survey of all admissions to the Radcliffe Infirmary in the years 1948–52 suffering from haematemesis, and finds that bleeding from oesophageal varices accounted for 23 out of a total of 540 such admissions (4.26%).

Cases with Liver Damage.—These have a very much worse prognosis than have the undamaged group. Such patients may already be far advanced in their disease before they bleed, and may be actually jaundiced. For this reason, because they lack thrombocytes, because they are also anaemic, and in consequence their metabolism is poor, haemorrhage is likely to be profuse. Such an event of itself seems to lead to hepatic incompetence and death from liver failure.

Cases with Liver Damage (14)

Age range	5–72 years
Injected as emergency	4
Lived days after first injection	1
„ weeks „ „ „	2
„ months „ „	4
„ one year or more	7
Not traced	1
Longest survival	7½ years
Average number of injections	3

Cases Without Liver Damage.—The occurrence of portal hypertension in this group is sometimes obscure in origin. A thrombosis of the portal vein or of the splenic vein must be postulated. One patient in this series had had a retrocaecal appendicitis, with localized peritonitis, and later a cholecystectomy for gall-stones. Another patient had had tuberculous peritonitis which had been cured by streptomycin. A third had received a blow in the abdomen in a motor accident. A fourth was a boy aged 5 years who had had haematemeses since the age of 2 years; in his case it must be supposed that a thrombosis had ascended from the umbilical vein through the ductus venosus to the portal vein.

Cases without Liver Damage (16)

Age range	5–60 years
Injected as emergency	0
Not traced	1
Alive and well	14
Longest survival	11 years
Average number of injections	7
Subsequent shunts	2

Technique

The technique employed in the present series has varied somewhat as to detail, but has conformed generally with that described in 1949 (Macbeth, 1951). The sclerosing fluid has latterly been sodium morrhuate 5%, and 3–4 ml. has been injected at each venepuncture. No harm seems to come of making about six injections of this size at any one session.

A general anaesthetic is given, and the largest Negus type oesophagoscope which can be passed is used. It is important to use as large an oesophagoscope as possible, because thereby the veins are put upon the stretch, and because the oesophagoscope can be used to obliterate the vein after injection by passing it beyond the injected point. Theoretically the varices nearest the cardia should be injected first. This should be done if a patient has bled recently, when the offending vein can often be recognized and injected above and below the bleeding point. But in a quiescent phase it is more convenient to take the veins in groups from above downwards.

A long needle-carrier, mounted upon a bayonet-type fitting and locking into a 10- or 20-ml. syringe, is used. The needle is screwed into the distal end of this and should be very sharp. The vein is steadied on the stretch by the beak of the oesophagoscope, and the needle is slid down the wall of the tube until it punctures the vein. The sodium morrhuate is injected and, with the needle still in place, a "mastoid strip" of gauze is passed downwards in an alligator forceps and pressed upon the vein. The needle is withdrawn and the gauze held in place for a full minute. The oesophagoscope is slid downwards for a centimetre or so and the manœuvre is repeated four or five times.

In cases where there is marked bleeding as a result of venepuncture or where the injection therapy is undertaken as an emergency measure during an active haemorrhage, the bleeding can usually be controlled after injection by some form of hydrostatic bag. The simplest form is the Miller–Abbott bag, but this suffers from the disadvantage that it is made of very thin rubber which readily tears. A useful bag is that known as the Sengstaken triple lumen tube. This has two fluid compartments, the smaller of which is the distal and passes into the stomach, and the larger fills and stretches the lumen of the oesophagus. It is inflated with normal saline and left in position for one to two hours.

The routine is to repeat the treatment every one to two weeks until no veins remain uninjected. The patients are then examined after three months and, if no varices are found, in a further six months. They are then examined every six or twelve months according to whether they show new varices.

Possible Complications

Further and Immediate Haemorrhages.—These can be avoided or controlled by the use of hydrostatic bags.

Ulceration.—This was seen in one case in which liver damage was considerable and where the outlook was probably hopeless.

Substernal Pain.—This is usual, but slight.

Venous Embolism.—This has not been seen.

Allergy to the Injection Fluid.—This has not been seen.

Discussion

Reynell (1951) points out that where adequate transfusion therapy is available haemorrhage from varices in patients without liver damage is not so serious as was originally thought, and that the more severe the liver damage the worse the prognosis of a haemorrhage. Not only do patients with liver damage tend to bleed for haematological reasons, but the effect of a massive haemorrhage is in itself to "decompensate" the liver, and such patients die of hepatic coma. At best, therefore, a haemorrhage may have a high nuisance value, and at worst it may result in death.

It has been fashionable among writers on the surgery of portal hypertension to dismiss thrombosing injections as not having justified themselves, and as unlikely to do so because new venous channels continually open up (Walker, 1949; Whipple, 1949; Learmonth, 1951). It may well be that those who make the first contention have remained in ignorance of successful work in this field because this has been published in otolaryngological journals; or possibly they may have become distrustful of unsatisfactory techniques. The contention about new venous channels must surely apply with equal force to any operation involving gastric or oesophageal transection and ligation of veins, with resuture.

As has been said, the veins of the oesophagus are specially apt to dilate in an attempt to carry the portal blood into the systemic venous channels, and one would imagine that, with the exception of those prolapsing into the lumen, they are in fact serving a useful purpose and should be given every encouragement to continue.

The only veins, therefore, which are a danger to the patient and whose control is necessary are the subepithelial veins. Whether they are subepithelial *ab initio* or are in reality submucous veins which have become more superficial is immaterial.

The thin-walled veins prolapsing into the lumen are obviously at risk, but it has not been determined why they bleed. Local injury by food, sepsis, sudden increase in intrathoracic pressure, and muscular movements have all been invoked. Digestion by regurgitated gastric juice has been suggested as a cause for erosion of these veins, but if this were so one would expect a greater incidence of bleeding from gastric veins, which does not seem to be the case. Learmonth (1951) rejects the acid-juice view and notes that haemorrhages often occur soon after physical exertion.

In the case of patients suffering from severe liver damage the results of injection therapy have been disappointing. It has often been possible to control a particular haemorrhagic incident and apparently to prolong life, but these patients readily pass into a vicious circle of liver damage with jaundice leading to haemorrhage, which in its turn seems to predispose to liver failure. In fact when patients admitted apparently with severe liver damage are controlled readily by transfusion and injection we begin to think that perhaps their portal hypertension is extrahepatic after all. It is always worth while to attempt to control even the least hopeful case, especially if active bleeding has recently occurred, until the diagnosis becomes clear or until the patient goes into liver failure.

In the group of patients without demonstrable liver damage the outlook is very different. All of the cases quoted have remained alive and well from eleven years to four months after being controlled. Of these, three have had abdominal operations.

One patient who had been controlled by injection for six years bled again and had a porto-caval shunt. This was unsuccessful, so he had a gastric transection. He later had no varices.

A second patient bled again at about the time he was due for oesophagoscopy; he was taken into another hospital, where he had a porto-caval shunt. This man reported that he was well.

A third patient was sent by her physician after one injection to a surgeon, who did a porto-caval shunt. Her spleen was not removed, and recent oesophagoscopy showed no further development of varices.

When controlled these patients are so well that they can live normal lives—one, a schoolboy, plays football and is a cross-country runner; another is a hospital nurse; others lead full and ordinary lives. The main disadvantage of this method is that the patients need to be oesophagoscoped once or twice a year as a routine, and this must be firmly emphasized. Kempe and Koch (1954) have noted that patients who fail to attend for examination may be running a risk. I would echo this, and would instance the case of a man who had been well for three years, but not checked by oesophagoscopy in that period. He was examined in March, 1955, and found to have a number of varices which needed injection. Further experience may show that some of these cases can be completely and permanently cured.

I would also agree with the observation made by the same writers that splenectomy is a valuable adjunct to injection therapy. If bleeding has recently occurred it is best to inject such veins as were probably responsible, then to have a splenectomy done, and finally to complete the injection course. This was the method employed in a number of cases, and it was noteworthy how much more controllable were the varices after splenectomy. If bleeding has not occurred recently the operation may immediately precede an injection course, as recommended by Kempe and Koch.

Size and profusion of varices in the oesophagus should not deter one from attempting injection, provided that the patient is a hopeful case otherwise; in fact one of the most successful cases in this series presented numerous veins the size of a fourth finger when first seen. But, as a prophylactic measure, it may be advisable in such cases to leave a hydrostatic bag in the oesophagus for two hours after injection.

In conclusion, I would say that sclerosing injections of oesophageal varices in combination with splenectomy provide a method of treatment which may palliate hopeless cases of liver damage, and which should be considered as a safe and satisfactory alternative to more complicated and hazardous procedures in cases of extrahepatic portal hypertension.

Summary

Portal hypertension indicates an increase of pressure within the portal venous system; this may be intrinsic due to liver disease, or extrinsic due to a thrombosis of the portal vein or a main radicle.

In both types of case the most troublesome symptom is haematemesis due to rupture of oesophageal varices. In intrinsic cases the cause of death is almost always liver failure, but this may be precipitated by a massive haemorrhage. In extrinsic cases patients may be incapacitated solely by the haemorrhages.

Treatment is aimed at preventing haemorrhage. Splenectomy alone gives temporary relief. Ligature and transection of veins and viscera may lead to opening of new channels. Venous porto-caval shunt operations are the most logical method of relieving portal pressure, but not minor procedures.

The only veins at risk are those prolapsing into the oesophageal lumen. Sclerosing injections of such varices are capable of controlling them indefinitely in extrinsic cases, and for limited periods in intrinsic cases. It is emphasized that patients must submit to oesophagoscopy once or twice a year, because new varices may form.

Experience in 14 cases with liver damage (intrinsic) and 16 cases without (extrinsic) is discussed and injection technique is described.

Splenectomy makes the veins more readily controllable, and should be carried out as an adjunct to injection therapy.

The method is a safe and satisfactory alternative to major surgery.

I am indebted to the physicians of the United Oxford Hospitals and other colleagues who have kindly invited me to treat their patients in this way, and in particular to Professor Leslie Witts, who has provided more of them than any other. I also acknowledge with gratitude the permission given by my colleague, Mr. Gavin Livingstone, to include in this series seven patients treated by him. Finally, I should like to record my thanks to Dr. Hugh Cowdell, of the department of pathology, for his kindness in making the photomicrographs.

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The total number of epileptics on the register of disabled persons was 16,267, or nearly 2% of the total register, said Sir GODFREY INCE, Permanent Secretary, Ministry of Labour and National Service, in his address at the annual general meeting of the British Epilepsy Association in June. The decrease in the total number of unemployed on the register over the past five years was 103, a disappointing figure, though it was affected by the number of newly registered epileptics. The decrease in the number of the severely disabled unemployed was 343; this was due in great part to the fine work of Remploy Ltd., who employ over 400 epileptics in special factories for the severely disabled. The Ministry gave about 300 epileptics a year an eight-weeks course at the industrial rehabilitation units, and over 80% of the 250 who completed it were placed in employment or training. Sir Godfrey pointed out that once an epileptic "appreciates that a fit is not going to cause consternation to anyone, a steady improvement sets in and the frequency and duration of the fits diminish. With many, the fits disappear entirely."

POTASSIUM AND PARALYSIS

BY

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AND

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This paper presents a further case of the uncommon but striking syndrome of hypokalaemic periodic paralysis associated with potassium-losing nephritis. A similar case, together with a review of previously published cases known or considered to be examples of this syndrome, has recently been reported (Evans and Milne, 1954).

Case Report

The patient, a housewife, was first admitted to hospital in November, 1948, when she was 34 years old, with a three-months' history of giddiness. She was found to be moderately hypertensive (B.P. 210/130). There was no past history of renal disease. Albuminuria was present, and a few hyaline casts were seen in the centrifuged deposit of the urine. Urea clearance was 103%.

The patient kept quite well until she was seen again in the out-patient department on August 3, 1953. She then gave a two-weeks history of pain behind the right eye. Her blood pressure was unchanged. She had partial third and fourth cranial nerve palsies on the right. She was admitted to hospital, and on September 3 she lost consciousness following an exacerbation of her headache and was found to have had a subarachnoid haemorrhage. On September 18, after a right carotid arteriogram, which showed a small aneurysm at the origin of the posterior communicating artery, the right common carotid artery was ligated.

She was seen from time to time as an out-patient, and in June, 1954, complained of some intermittent weakness and cramps in her arms and legs. On questioning, she admitted to similar symptoms occasionally for about six years. She also had slight premenstrual swelling of the ankles. Physical examination revealed no fresh abnormality.

TABLE I

	Nov. 10 1948	Nov. 16 1954	Nov. 25 1954*	Dec. 1 1954†	Dec. 2 1954‡	Feb. 10 1955
Blood urea (mg./100 ml.)	20	34			31	34
Urea clearance (%) ..	103	58				
Basal metabolic rate (%)		+3				
24-hr. urine:						
Total protein (mg.) ..		540				
Potassium (g.) ..		2·2				
Serum cholesterol (mg./100 ml.)		156				
Serum sodium (mEq/l.)..		142	144	149	142	
,, potassium (mEq/l.)		2·6	2·5	4·6	3·1	2·2
,, chloride (mEq/l.)		94	97	109	102	
Alkali reserve (mEq/l.)..		32	31	31	29	33
Serum calcium (mg./100 ml.)			12·2	10		10·6
Serum phosphorus (mg./100 ml.)			2·7	3·1		
Serum alk. phosphatase (K.-A. units/100 ml.)..			8·5			
Serum protein:						
Total (g./100 ml.) ..			8·4			
Albumin (g./100 ml.)..			5·6			
Globulin (g./100 ml.)..			2·8			

* Day before balance. † Third day of potassium supplement. ‡ Day after potassium discontinued.

TABLE II.—*Urinary Acidification Test.* (5 *g.* (94 *mEq*) *Ammonium Chloride Given at* 9.45 *a.m.*)

Time:	9.45 a.m.	11.45 a.m.	1.45 p.m.	3.45 p.m.
pH of urine	6·9	7·2	6·9	7·0
Ammonia (mEq/hour)	0·61	2·1	0·9	1·2

In October she said that her "fingers had dropped" in an attack of weakness. The attack lasted a few hours. She was asked to attend immediately she had another attack, and was seen next on November 3. She then had paralysis of the extensors of the fingers of the left hand and weakness of plantar flexion of the right foot, with absence of the corresponding tendon reflexes. This attack lasted about 24 hours. There were no sensory changes. Direct electrical stimulation of the extensors of the fingers of the left hand failed to produce any response. Electromyograms showed no spontaneous activity, and a reduced number of small and polyphasic motor unit potentials on volition. A diagnosis of periodic paralysis was made. Trousseau's sign was positive when there was periodic paralysis (Fourman and McCance, 1955) or when there was marked muscle weakness. Although the patient complained of cramps at these times there was no spontaneous tetany.

There was no family history of any similar attacks. Attacks could not be provoked by large carbohydrate meals, insulin (up to 16 units soluble insulin only, because of the danger of a more profound hypokalaemia), cold, or exercise, although the patient said that the attacks tended to follow unwonted exertion on previous days.

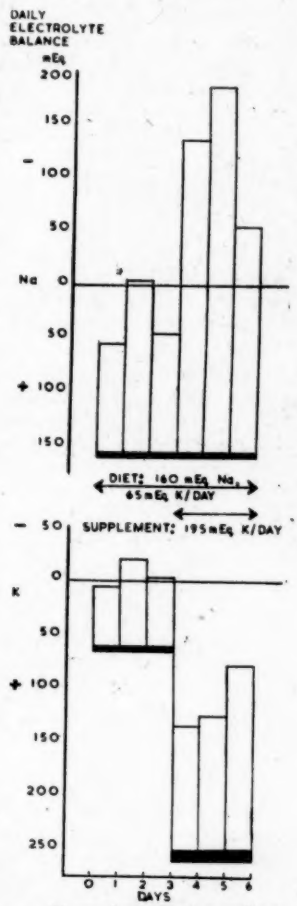

Chart showing the sodium and potassium balance.

Further investigations revealed a persistently lowered serum potassium at about 2.5 mEq (normal 3.9–5.2 mEq). Serum cholesterol, sodium, chlorides, calcium, phosphorus, alkaline phosphatase, urea, and alkali reserve were consistently normal. Plasma proteins were normal. Urea clearance showed an average value of 58%. There was 0.5 g. of protein per 24-hour urine (Table I). Maximum urine concentration was to S.G. 1016 only. Ingestion of 5 g. of ammonium chloride caused no increase in the acidity of the urine during the following six hours, although there was a moderate increase of ammonia production (Table II). The intravenous pyelogram was normal. The plasma hydrocortisone was within normal limits at 5.5 μg. per 100 ml. No aldosterone could be detected in the plasma. The salivary sodium/potassium ratio was also normal at 0.42. A sodium and potassium balance was carried out with a diet containing 65 mEq of potassium and 160 mEq of sodium daily (see Chart).

During the first three days there was no gross evidence of lack of equilibrium of sodium or potassium. Then 195 mEq of potassium was added as 3 g. of potassium chloride five times daily. There was immediate excretion of sodium and marked retention of potassium, suggesting replacement of an intracellular potassium deficit which had been partly compensated for by a raised intracellular sodium. The serum potassium rose to 4.6 mEq/litre. The serum potassium fell immediately the supplement was stopped.

During the time of the potassium supplement the patient said that she felt fitter than she had done for many months, and lost all her residual muscle stiffness.

Electrocardiograms showed changes consistent with hypokalaemia (Schwartz *et al.*, 1954; McAllen, 1955) during the attacks of paralysis. These changes were not evident during the period of potassium supplement.

Comment.—This case illustrates the classical features of the periodic paralysis syndrome—namely, intermittent paralysis associated with absence of the tendon reflexes in the affected muscles. The absence of reaction to direct electrical stimulation of the affected muscles confirmed the diagnosis. The persistent hypokalaemia and the response to potassium therapy indicated that this was in fact a case of hypokalaemic paralysis. The disturbed kidney function shown by the common tests of renal function, the negative potassium balance, and the otherwise normal blood chemistry indicate potassium-losing nephritis. It seems likely that the renal changes were secondary to benign hypertension and not to pyelonephritis as in similar reported cases. Primary aldosteronism was excluded by the absence of detectable aldosterone in the plasma.

Discussion

The syndrome of periodic paralysis has been reported in association with hypokalaemia and in other conditions with no apparent disorder of potassium metabolism. The classical example is family periodic paralysis (Talbott, 1941). In this condition hypokalaemia is typically present only during the paralytic attacks. Since there is no loss of potassium from the body, it is assumed that there is movement of potassium into cells (Danowski *et al.*, 1948). Swelling of the affected muscles has been noted during attacks. Histologically, swelling of muscle fibres with vacuolation is seen (Bickerstaff, 1953). Hypokalaemic periodic paralysis has also been noted in the recovery phase of diabetic coma (Nabarro *et al.*, 1952), thyrotoxicosis (Weissman, 1952), porphyrinuria (Thompson and Parrish, 1953), the Fanconi group of syndromes (Milne *et al.*, 1952; Bickel *et al.*, 1953), potassium-losing nephritis (Evans and Milne, 1954), the diuretic phase of acute tubular necrosis (Bull *et al.*, 1949), uretero-colic anastomosis (Diefenbach *et al.*, 1951), sprue and Addison's disease over-treated with deoxycortone acetate (Black, 1953), liquorice and para-aminosalicylate administration (Cayley, 1950; Strong, 1951), and now in primary aldosteronism (Conn, 1955).

Clinically, there is an acute onset of flaccid paralysis which commonly affects, primarily or solely, the extensor muscles of the limbs. The bulbar and respiratory muscles are usually spared, and there is no sensory loss. The electromyogram (E.M.G.) shows that the muscle is inexcitable either directly or through its motor nerve (Adams *et al.*, 1953a).

Periodic Paralysis with Uncertain or No Known Relation to Potassium Metabolism.—Otherwise typical family periodic paralysis has been reported in which no abnormality of potassium metabolism could be demonstrated (Tyler *et al.*, 1951; *J. Pediat.*, 1953). Periodic paralysis has also been reported in association with adiposo-genital dystrophy (Prader and Zellweger, 1952), dystrophia myotonica (Bredemann, 1952), and after meningitis (Kjerulf-Jensen *et al.*, 1951). In the post-meningitic case and the patient with adiposo-genital dystrophy there was a persistent hypokalaemia. It is possible that these attacks may be due to disturbances of hypothalamic electrolyte-regulating centres.

Hyperkalaemic Paralysis.—Widespread paralysis has been noted in the terminal stages of uraemia, with hyperkalaemia (Merrill *et al.*, 1950; Bull *et al.*, 1953). Similar paralysis has been induced in the over-treatment of hypokalaemia by intravenous potassium salts (Finch *et al.*, 1946). It is possible that hyperkalaemia may also contribute to the paralysis in paroxysmal myohaemoglobinuria (Buchanan and Steiner, 1951) and the crush syndrome (Oliver *et al.*, 1951). Clinically, there is usually a symmetrical ascending flaccid paralysis. It is frequently fatal from acute respiratory failure. Increased myotatic irritability and increased tendon reflexes have been noted: also paraesthesiae and objective sensory loss. These findings are all in contrast to those in hypokalaemic paralysis.

Relation of Potassium to Paralysis.—In hypokalaemia there is no constant relation between the serum level and the site or extent of the paralysis or even its occurrence. In hyperkalaemia there is a much closer correlation.

In family periodic paralysis it is generally assumed that the defect is at the muscle membrane (Adams *et al.*, 1953b). However, we have been unable to find any reports of nerve-conduction studies in family periodic paralysis or in other hypokalaemic syndromes. It is possible that there may also be a conduction defect in the peripheral nerve or even at a higher level, although the distribution does not usually suggest a nerve lesion.

The possibility of peripheral nerve or central nervous system dysfunction seems more likely in hyperkalaemic paralysis, where sensory changes have frequently been reported.

Summary

A case of potassium-losing nephritis with periodic paralysis is described.

Hypokalaemic and hyperkalaemic paralysis and related conditions are discussed.

The relation of these conditions to potassium metabolism is considered.

We wish to thank Dr. Thompson Hancock for permission to publish. We also thank him and Drs. Helen E. Dimsdale, A. T. Richardson, and D. N. Baron for much help and useful criticism; also Dr. O. Garrod for the aldosterone estimation.

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The Israeli Ministry of Health has marked the occasion of the Third World Congress of the Israeli Medical Association by publishing a pamphlet entitled *Israel Health Services*. This traces the growth of these services from the department set up by the British Civil Mandatory Administration. Voluntary health organizations substantially helped the Ministry, and in 1954 W.H.O. aid totalled 34,800 dollars. At first the unrestricted flow of unselected immigrants caused an acute shortage of medical staff. By June, 1955, however, there was one doctor per 440 of population. Much has been accomplished during the first seven years: the incidence of typhoid, diphtheria, typhus fever, tuberculosis, and venereal disease has fallen considerably. Acute poliomyelitis is now the chief problem. Most of the cases are in children under 5 years of age.

TREATMENT OF CHRONIC LEAD-POISONING WITH CALCIUM DISODIUM VERSENATE

BY

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AND

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The treatment of lead-poisoning by the use of intravenous calcium disodium ethylenediamine tetra-acetic acid (E.D.T.A.; versenate) has been described by several authors in America, both in children (Byers and Maloof, 1954; Bessman *et al.*, 1952, 1954; Karpinski *et al.*, 1953) and in adults (Belknap, 1952; Sidbury *et al.*, 1953; Hardy *et al.*, 1954). The first report from this country has been published recently (Giles *et al.*, 1955). All authors agree that treatment with versenate gives prompt relief from the distressing symptoms of lead-poisoning.

Calcium disodium versenate is a synthetic chelating agent that removes lead from the body by the formation of a soluble non-ionized lead complex which is excreted in the urine. The pharmacology and mode of action of versenate are described in detail by Karpinski *et al.* (1953).

In chronic lead-poisoning lead is stored in the bones, and this may subsequently be released by infection or metabolic stress and cause acute lead-poisoning (Aub *et al.*, 1925). It has been shown that lead can be mobilized by the administration of ammonium chloride or "para-thor-mone" (Hunter and Aub, 1927). However, such treatment may also cause a recurrence of the symptoms of lead-poisoning, and opinion is divided, therefore, on the wisdom of attempts to de-lead the skeleton (Cantarow and Trumper, 1944). It is possible that during treatment with versenate most of the lead excreted in the urine is derived from the body fluids and soft tissues, and that lead deposited in the skeleton is less readily accessible. For this reason, Giles *et al.* (1955) have tried treatment with versenate and ammonium chloride, but they did not obtain an increase in the rate of excretion of lead in the urine above that produced by versenate alone.

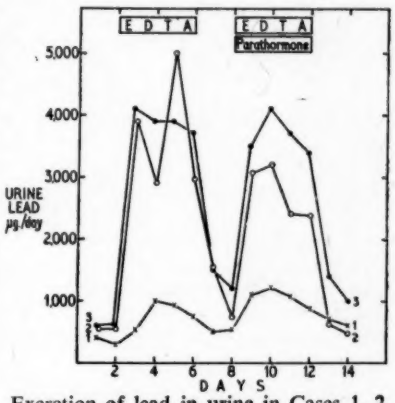
This paper describes the excellent results obtained by the use of versenate in three patients with chronic lead-poisoning. In addition, an attempt was made to mobilize lead stored in the bones and to increase its rate of excretion in the urine by the simultaneous use of para-thor-mone and versenate.

Case 1

A man aged 33, employed as a vitreous enameller for seven years, was referred to U.C.H. with complaints of anorexia, constipation, and headaches over the past year, and recently of repeated attacks of abdominal pain which lasted for hours and doubled him up. His doctor had successfully treated these attacks with intravenous calcium gluconate. The patient had also noticed an unpleasant taste in his mouth, that the grip of his left hand was weak, and that he had difficulty in concentration, as though "a cloud was over my brain." There was a well-developed lead line on the gums, but no distinct pallor of the skin. The B.P. was 140/80 and there were no objective abnormalities in the central nervous system other than a coarse tremor of the hands. Before treatment he was observed to have several attacks of colicky pain in which the abdomen became rigid.

Laboratory Tests.—Hb, 80%. Punctate basophil count, 11,200 per million red blood cells. Urine: albumin +; sugar 0; no excess of amino-acids. Qualitative tests for coproporphyrins ++. Blood urea, 48%; urea clearance, 106%. Urine lead, 400 and 300 μg. a day.

Two four-day courses of versenate were given, separated by two rest days. Dosage: 2 g. of versenate dissolved in one litre of normal saline given intravenously over nine hours (0.3 g./30 lb. (13.6 kg.) body weight a day). Para-thor-mone, 150 U.S.P. units a day intramuscularly, was given during the second course. The excretion of lead in the urine is shown in the Chart. The headaches, tremor, and colic were rapidly relieved. The lead colic returned on the third day of para-thor-mone injections, but was again relieved within 30 minutes of starting the versenate drip, and did not return. The excess urine coproporphyrins had disappeared by the end of treatment.



Excretion of lead in urine in Cases 1, 2, and 3.

Two months later the patient said that he still felt better than he had for years, and had gained 12 lb. (5.4 kg.) in weight: Hb, 110%; punctate basophil count less than 1,000 per million red blood cells; qualitative tests for urine coproporphyrins, negative; no albumin.

Case 2

A man aged 42, employed as a vitreous enameller for three years in the same factory as Case 1, complained of ill-health, lack of concentration, irritability, and headaches over the past six months. He had a bad taste in the mouth, a poor appetite, habitual constipation, and suffered from occasional attacks of abdominal pain, which were not severe. He was a thin, unhealthy-looking man with extensive gingivitis and a lead line on the gums. B.P. 140/70. The only abnormality found in the C.N.S. was a tremor of the hands.

Laboratory Tests.—Hb, 92%. Punctate basophil count, 4,000 per million red blood cells. Urine: no albumin, no sugar, no excess of amino-acids. Qualitative test for coproporphyrins +++. Blood urea, 33 mg. per 100 ml. Urea clearance, 94%. Urine lead, 540 and 540 μg. a day.

The treatment was as in Case 1, except that the dose of versenate was 4 g. a day, which was 1 g./30 lb. body weight a day. The excretion of lead in the urine is shown in the Chart. The symptoms were completely relieved by the end of the first course of treatment and there was then no excess of urine coproporphyrins. Six weeks later the patient still felt very well: Hb, 98%; punctate basophil count, less than 500 per million red blood cells; urine: no excess of coproporphyrins; no albumin.

Case 3

A man aged 47, a vitreous enameller employed for nine years in the same factory as Cases 1 and 2, had previously been treated for lead-poisoning in 1950 at the London Hospital. He attended U.C.H. for screening tests with other employees, but at that time had few spontaneous complaints. Because of a strongly positive qualitative test for urinary coproporphyrins he was offered treatment, but was unable to accept as his wife was ill. Subsequently he reported sick

with abdominal colic and was admitted for treatment. He then admitted to general malaise, constipation, and milder attacks of abdominal pain for the past four months. There was no pallor and no lead line, the patient being edentulous. The B.P. was 160/90; there was a coarse tremor of the hands, otherwise no abnormality in the C.N.S.

Laboratory Tests.—Hb, 88%. Punctate basophil count, 2,000 per million red blood cells. Urine: albumin +; no sugar and no excess of amino-acids. Qualitative tests for coproporphyrins ++. Blood urea, 38 mg. per 100 ml. Urea clearance, 140%. Urine lead, 560 and 610 μg. a day.

The treatment was the same as in Case 2. Versenate dosage 4 g. a day (0.8 g./30 lb. body weight a day). The excretion of lead in the urine is shown in the Chart. The symptoms were completely relieved and the patient felt very well by the end of the second course of treatment: Hb, 97%; punctate basophil count, less than 500 per million red blood cells; qualitative test for urine coproporphyrins negative.

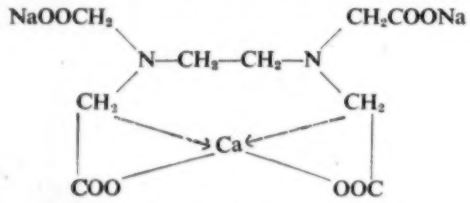
Methods

Lead.—Lead determinations were carried out at the M.R.C. Unit of Industrial Toxicology by the method recommended in the Report of the Lead Panel (1954). Normal values for lead excretion = <80 μg. Pb a day. Upper values for lead workers = 250 μg. Pb a day.

Coproporphyrins.—Three drops of hydrogen peroxide, 5 drops of glacial acetic acid, and 1–2 ml. of ether were added to 5 ml. of fresh urine in a test-tube and shaken. After ten minutes the ether layer was examined under Wood's lamp for the characteristic reddish-pink fluorescence.

Discussion

Calcium disodium versenate is the calcium complex of a synthetic amino-acid, ethylenediamine tetra-acetic acid:



The nitrogen atoms donate electrons to metals, completing their atomic configuration, and in this way form stable ring structures in which the metal is non-ionized. The bonds indicated by the arrows are responsible for the poor ionization. Metals such as lead, copper, and nickel are bound or chelated more firmly than is calcium and displace it from the complex. Fortunately, essential elements such as iron, copper, and cobalt are fixed even more strongly by the tissues, and the administration of calcium disodium versenate does not appreciably increase the rate of excretion of these metals from the body; furthermore, the plasma concentration of calcium, magnesium, and sodium is not significantly altered by this treatment (Cotter, 1954; Spencer *et al.*, 1952). The metal, when chelated, is freely soluble and is readily excreted in the urine, but as it is not ionized it does not exhibit its usual chemical and pharmacological properties (Cotter, 1954).

In the treatment of heavy metal poisoning the calcium complex is used, as versenate alone combines with calcium in the plasma and if given in large doses may cause hypocalcaemic tetany and death (Popovici *et al.*, 1950; Spencer *et al.*, 1952). Animal experiments have shown that calcium disodium versenate is relatively non-toxic and has a high therapeutic index (Bauer *et al.*, 1952). The intravenous LD_{50} for rats is 3,000 mg. per kg., compared with the effective therapeutic dose of less than 50 mg. per kg. per day. In patients few toxic reactions have been reported from the use of calcium disodium versenate. Transient depression of the bone marrow occurred in one case (Belknap, 1952), and T-wave changes in the electrocardiogram were demonstrated by Bradley and Powell (1954).

Calcium disodium versenate can be given by mouth and does not to any extent chelate heavy metals present in the gut (Bradley and Powell, 1954; Cotter, 1954). However, it is much more effective when given intravenously. When versenate labelled with ^{14}C was given intravenously 90% was excreted within six hours (Foreman *et al.*, 1953b). This suggests that the most effective way of giving versenate is by a slow continuous intravenous infusion.

Dosage has largely been empirical, most workers following the recommendations of Foreman *et al.* (1953a)—namely, 1 g./30 lb. body weight/day at a maximum rate of 0.5 g./30 lb./hour intravenously, and not exceeding 5 g./30 lb./week. Since 1 mol of versenate can bind 1 mol of lead, the administration of 0.5 g. of versenate would, if 100% efficient, promote the excretion of 260 mg. of lead. However, the maximum observed excretion of lead during treatment with versenate has been 4 mg. a day in children (Giles *et al.*, 1955) and 10 mg. a day in adults (Hardy *et al.*, 1954), an efficiency of only about 1%. Bessman *et al.* (1954) have suggested that the reason for this low efficiency is that versenate has to compete for lead with other binding agents such as the sulphydryl group of proteins.

The three patients in this series responded very quickly to treatment with disodium calcium versenate, as did those previously reported. Relief from lead colic and from cerebral symptoms such as headache and irritability occurred within an hour of starting treatment, and the patients were completely free of symptoms by the end of two four-day courses. There were no toxic effects. The excess of coproporphyrins disappeared from the urine, the punctate basophil count gradually fell, and the haemoglobin returned to normal levels. The excretion of lead in the urine was greatly increased during the infusion of versenate and reached a maximum of 5 mg. of Pb a day.

The first patient who was given versenate in a dosage of 0.3 g./30 lb./day excreted much less lead in the urine than did the second and third patients, who were given 0.8 and 1 g./30 lb./day. The higher dose caused no ill effects and was much more effective in promoting lead excretion, probably because it was given in a very slow intravenous infusion over nine hours. Bessman *et al.* (1954) had reported that increasing the dose of versenate did not increase the excretion of lead, but in their observations it was given over a shorter period of time, and much of it may have been excreted in the urine before coming into equilibrium with lead in the tissues. It should be noted that the smaller dose of versenate was just as effective in relieving the acute symptoms of lead-poisoning as was the larger dose, and there was no recurrence of symptoms in this patient in the six months of observation following the period of treatment. It does not seem necessary to attempt the removal of all the lead stored in the body, and indeed this would probably need 10–20 courses of treatment.

Para-thor-mone and ammonium chloride have both been used to remove lead from the skeleton (Hunter and Aub, 1927). In the present series, combined treatment with calcium disodium versenate and injections of para-thor-mone did not cause a sustained rise in the excretion of lead in the urine greater than that obtained with calcium disodium versenate alone. However, there may have been an initial increase in the excretion of lead in the stools as in the cases reported by Hunter and Aub (1927). Giles *et al.* (1955) have reported that the administration of ammonium chloride and versenate to one patient did not result in an increased excretion of lead in the urine above that produced by versenate alone. The high rate of excretion of lead in the urine and the excellent clinical results obtained by treatment with calcium disodium versenate alone are so uniformly satisfactory that the use of acidifying agents or of para-thor-mone does not seem justified.

Summary

The use of calcium disodium versenate in the treatment of three patients with chronic lead-poisoning is described. This treatment rapidly relieved the symptoms

of lead-poisoning and promoted the excretion of large amounts of lead in the urine. No toxic effects were observed.

The administration of para-thor-mone during treatment with versenate did not increase the rate of excretion of lead in the urine above that obtained by versenate alone.

The chemistry, pharmacology, and method of use of versenate are discussed.

We wish to thank Dr. Donald Hunter, Dr. Lesley Bidstrup, and Mr. B. J. Biles, of the Medical Research Council Department for Research in Industrial Medicine, for the lead estimations; and Mr. V. K. Asta for the chart.

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TRICHOMONAS VAGINALIS INFECTION IN THE MALE

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In recent years fungi, viruses, spirochaetes, and protozoa have tended to displace the gonococcus in the causation of acute and chronic inflammation of the lower genito-urinary tract in both sexes, and for this reason more examples of such infections are now seen at urological clinics. Some authors believe that the types of trichomonads described—*Trichomonas vaginalis* (genital), *T. hominis* (intestinal), and *T. tenax* (buccal)—belong to one species only, their morphological differences arising from their particular human "habitat" (*Standortsvarietäten-Flaskamp*). But Wenrich (1947) suggests that the different trichomonads infesting man belong to distinct species. Despite occasional reports of trichomonal infection of the male urethra, such infection has been regarded for many years as affecting women only. However, with the increasing occurrence of residual post-gonococcal urethritis following adequate penicillin therapy, and the higher incidence of non-gonococcal urethritis in the male, *T. vaginalis* infection with its complications in both sexes is gaining wider recognition as a definite entity. Some authors (Pomeroy, 1948; Freed, 1948) refer to it as the "seventh venereal disease."

The Parasite and its Recognition

T. vaginalis is a pear-shaped, ovoid, or round pentaflagellated protozoon, 10–20 μ long by 8–10 μ broad, though much smaller forms, measuring 2 to 3 μ, are not uncommon. Four free flagella arising at the blepharoblast, part of the neuromotor system, emerge from the upper pole of the body of the parasite. The so-called fifth flagellum is attached to one of the borders of the body and forms part of the undulating membrane. Even the smallest forms have flagella, though occasionally only a single but very long, thin flagellum is present. Small, non-flagellated trophozoites have been observed; these are degenerative forms which recover their properties when they change habitat (Wenyon, 1926). Our own observations have led us to conclude that they represent evolutive forms of the life cycle.

In fresh preparations examined under dark-field illumination the free extremity of one or more flagella can be seen bending and unbending, inwards and occasionally outwards (Feinberg). This phenomenon can also be seen in fixed, unstained smears (Fig. 1). Occasionally in such preparations the flagella appear segmented. If fresh preparations are observed under dark-field illumination with interposed polarizing filters (Silva-Inzunza's technique), flagella appear coloured red. The flagellum of the undulating membrane is without colour, and for this reason we believe it to be an independent structure. Thus the parasite is really a tetraflagellate (Silva-Inzunza and Coutts, 1954). When fixed, unstained smears are examined under dark-field illumination a cystostome is clearly visible in the upper pole of the body of some parasites, the common axis from which flagella branch off emerging from the borders of this opening (Fig. 2). At the lower pole another opening may be seen, through which the axostyle, a pointed, more or less rigid structure of doubtful significance, is probably ejected. Intracytoplasmic structures—nucleus, blepharoblast, and parabasal body—are too well known to need description. Little is known about multiplication and development of *T. vaginalis*; multiplication may be by simple binary division or by budding (Fig. 3). Cysts and pseudocysts have also been described.

The presence of *T. vaginalis* in secretions or urinary sediment can be established by examination of fresh preparations or of unstained smears fixed in 10% formol. This last type of preparation has the advantage that the sample can be collected anywhere and sent to a laboratory for diagnosis. Fresh preparations can be viewed with simple, dark-field, or phase-contrast microscopy; fixed, unstained smears are best studied under sunlight or lamplight dark-field. Less satisfactory results are obtained with stained smears. In fresh preparations treated with 5% aqueous solution of fluorescein (vital stain) all living forms of the parasite rapidly assume a brilliant green colour (trophozoites, cysts, etc.). This technique is very useful when the material contains numerous pus cells and few trophozoites (Coutts and Silva-Inzunza, 1954).

Pathogenicity

The subject of the pathogenicity of *T. vaginalis* has been much discussed (Rodecurt, 1952). Some authors doubt or deny that it has pathogenic properties, others favour a facultative pathogenicity, while still others stress the influence of co-infectors (anaerobes, viruses, spirillae). The experiments of Trussell and Plass (1940), of Hesseltine and others in women, and those of Lanceley and McEntegart (1953) in men, however, have established beyond doubt the pathogenicity of *T. vaginalis*.

In adult males contagion is usually of a sexual nature. We have seen a few cases in prepubertal boys, mostly vagabonds living promiscuously. We have seen pederasts fortuitously infected by another who shortly before had been

anally fornicated by a married invert harbouring numerous *T. vaginalis* in the prostate. We have also seen two cases of infection following oral coitus; in both these the woman, a prostitute, had probably recently performed the same act with a client infected with *T. vaginalis* and still harboured living parasites in her mouth.

Some symptomless virgins and others with leucorrhoea harbour the parasite in their vagina before marriage; the husbands must promptly be infected, but seldom develop an acute urethritis. Only once have we seen a recently married man who during his honeymoon developed an acute trichomonal urethritis. On two other occasions men have consulted us with a mild urethritis appearing within the first month of their marriage; one of them had never previously had sexual intercourse, and the other regarded it as the recurrence of a former gonorrhoea. We have seen cases in which man and wife were infected but symptomless; the husband had intercourse with the wife of a friend, and shortly afterwards she developed an acute vulvovaginitis and intense cystitis, with numerous *T. vaginalis* in both the vaginal secretion and the urinary sediment. During the incubation period she had intercourse with her own husband, but he remained free of symptoms. On later examination *T. vaginalis* was found in the first sample of urine collected after prostatic massage.

Fig. 1

Fig. 2

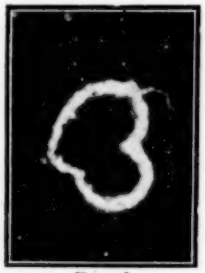

Fig. 3

Fig. 4

Photomicrographs taken under dark-field illumination (×900) of fixed, unstained smears of vaginal secretion from a case of *T. vaginalis* infection. Fig. 1.—*T. vaginalis* with flagella. Fig. 2.—Cystostome and caudal opening. Fig. 3.—Stage of division. Fig. 4.—Dichotomy of free extremity of flagella.

Superinfection is another interesting aspect; in two couples with latent *T. vaginalis* infection the husband, after extramarital intercourse with an infected woman, developed an acute trichomonal urethritis. During the incubation period he had intercourse with his wife, but she remained symptomless. Superinfection from heterogeneous sources is undoubtedly very common among men, but in our experience usually remains symptomless. A common source of infection is the carrier, in whom the parasite is apparently harmless, but it may become pathogenic when transmitted to other human beings. In only a very few cases could we attribute infection in males directly to fomites—such as the use of infected underwear or towels—or to direct extragenital contact with secretions containing the parasite, such as from water-closets.

In papers published in 1947 and 1952 some of us (Coutts, 1947) have tried to explain the processes of infection and of infestation on the basis of electrical phenomena such as was demonstrated by Fairbairn *et al.* (1946) in the case of certain trypanosomes. According to these latter authors trypanosomes with positive electrical charges penetrate red blood corpuscles with negative charges, while the parasites with negative charges are repelled by the erythrocytes. In the above-mentioned papers we reported the frequent presence of vibrating polymorphonuclear leucocytes in fresh preparations containing spirochaetes or protozoa observed under dark-field illumination, owing to intense brownian movement of intracytoplasmic granules. We tried to explain this intense motility of the granules on the basis of their like electrical charge which causes them to repel each other. This charge would be of the same type as that possessed by the invader, and the phagocyte is thus repelled, kept in constant intracytoplasmic activity, fatigued, and killed. According to this hypothesis the latent and carrier stages would signify an electrical equilibrium between parasite and organism.

Infection in Males

Many thousands of cases of male genito-urinary trichomoniasis have been reported in the past decade. Since 1937 (Coutts and Monetta, 1938) we have studied genito-urinary trichomoniasis in both male and female at the Urologic Clinic of the School of Medicine, Chile University, and at the Central Antivenereal Policlinic of the National Health Service (Coutts, 1942, 1948). Between 1951 and 1954 we have seen in the clinic and privately some 8,329 male cases of urethritis, 5,847 with gonorrhoea and 2,482 (29%) non-gonococcal. Amongst the latter *T. vaginalis* was found in 1,690 cases (68%).

In the male, infection by *T. vaginalis* may occur alone or in association with gonococcal, fungal, viral, spirochaetal, or other infections, and clinically may be acute, chronic, or latent.

Acute Infection

It is not always possible to be certain that an acute urethritis is an initial trichomonal infection, as it may be a flare-up of a chronic process. Of the 1,690 cases, we have classified only 262 (15.5%) as acute primary trichomonal urethritis when the patient was seen within the first five days after the appearance of an intense discharge and after a careful urological investigation we were unable to find the parasite in the prostatic fluid.

The incubation period varies from three to eight days (Coutts and Silva-Inzunza, 1952; Silva-Inzunza and Coutts, 1953). Urethral discharge is the first objective symptom, which may or may not be preceded by an itching sensation around the urinary meatus or a slight burning on micturition. The discharge may be slight and watery or milky in appearance, or be abundant and purulent as observed in gonococcal infection. This last type is frequently accompanied by preputial oedema and intense burning during urination. Painful erections are occasionally present.

We recommend the simultaneous study under dark-field illumination of a Gram-stained smear and a fresh preparation of the urethral discharge in all cases. Mild trichomonal discharges contain epithelial cells in large numbers, numerous leucocytes, and actively motile parasites. Discharges containing large numbers of pus cells must be diluted before observation, as recommended previously (Coutts and Silva-Inzunza, 1954). Some authors have remarked the frequency of erythrocytes in trichomonal discharges, but according to our observations this has no pathognomonic significance. If the discharge is slight, the urine is clear in both glasses but contains numerous heavy threads in the first; when the discharge is very profuse, the urine is cloudy in the first glass and clear in the second.

In untreated cases the posterior urethra and prostate may be rapidly invaded: a sensation of weight in the perineum, dysuria, and varying degrees of tenesmus mark the invasion of these structures. We have observed several cases of prostatitis and one of prostatic abscess for which *T. vaginalis* was alone responsible. These complications are not accompanied by fever. Urine is cloudy in both glasses.

Acute epididymitis as a possible complication of genito-urinary *T. vaginalis* infection is still disputed by many authors. Only a few cases have been described, and we ourselves have seen three cases in which this complication developed during an untreated acute primary infection.

Onset and evolution are similar to those of pyogenic epididymitis of urethral origin, but the vas deferens is little enlarged, and fever is slight or absent. Acute inflammation of the seminal vesicles during this stage is rare. In some cases acute cystitis sets in; pus cells and numerous *T. vaginalis* are found in an otherwise sterile urine. Some authors have reported simultaneous arthralgias, others arthritis or polyarthritis during the acute stage, and these symptoms have also been observed by us. The parasite has been found in the preputial sac whether local inflammatory signs have been present or not. Out of a group of 40 cases of acute balanitis studied by Lanceley and McEntegart (1953), in only one was the parasite not found in some part of the urogenital tract. We have seen three such cases, all associated with large numbers of spirilla.

Chronic Infection

Chronic infection with *T. vaginalis* is very common. We estimate that 85% of cases studied by us can be classified as chronic. *T. vaginalis* survives in the human host possibly by adaptation of structure, biochemistry, and life cycle. For reasons unknown most of these patients occasionally have a mild or intense urethral discharge, or the sudden appearance of acute prostatitis, epididymitis, or cystitis. It is often impossible to establish whether such cases are due to true reactivation or to superinfection from a heterogeneous source. The most common form of chronic infection is the morning drop containing a moderate number of pus cells, large numbers of epithelial cells, and actively motile *T. vaginalis*. Other cases present no urethral discharge, but numerous threads occur in the first portion of an otherwise clear, transparent, sterile urine, these threads containing pus cells and *T. vaginalis*.

Infection of the prostate is variable; Silva-Inzunza (1948) gives an incidence of 3%, and Turteltaub (1954) one of 20.9%. Like other authors, we have also found *T. vaginalis* in the prostatic fluid of a high proportion (40%) of husbands whose wives harbour the parasite in the vagina. Many of these males have never had a urethral discharge, but most of them have threads in the urine (Coutts and Silva-Inzunza, 1948). Of 182 men over 60 years of age investigated for cancer, dark-field examination of prostatic fluid revealed *T. vaginalis* in five (2.7%). In only one of these cases were pus cells present.

Ejaculatio praecox may be diagnosed in men with chronic trichomonal prostatitis, this symptom in some cases being the starting-point of a sexual neurosis; urinary symptoms such as imperative micturition and periods of dysuria also occur. Mild cystitis has also been observed; in such cases a moderate number of pus cells and some red blood cells as well as *T. vaginalis* are found in the sediment of bladder urine.

We have found the parasite in recently ejaculated semen in four cases of recurrent haemospermia; in three only a moderate number of pus cells were seen, but in the fourth case they were abundant. Culture of the spermatic fluid in all cases gave only a few colonies of bacteria considered to be of secondary importance. Chronic spermato-cystitis has been described, and Vargas-Zalazar, in over 1,000 sperm-cell counts in cases of infertility, has found pus and *T. vaginalis* in three.

Of greater interest is the sudden appearance of a subacute or acute inflammation of the epididymis in patients with clear or slightly cloudy urine containing a few pus cells but no bacteria. As in the form complicating acute infection, the vas deferens is not, or only very slightly, enlarged, and the corresponding seminal vesicle is usually normal on palpation and painless. Fever, if present, is very slight. The evolution is slow, and the clinical picture may suggest tuberculosis. Before the present study we had found *T. vaginalis* in scrapings of the surface of the epididymal canal in three cases of non-specific epididymitis. In one of these we observed the parasite in unstained sections of tissue examined under dark-field illumination (Coutts *et al.*, 1952). In the past two years we have carefully studied 30 cases of non-specific epididymitis before and after epididymectomy (Saavedra, 1954). In six cases the parasite was found in urethra and prostate, and in three of these in scrapings of the removed structure. In all three cases culture of epididymal tissue in appropriate media was sterile.

Many patients, especially women, suffering from chronic *T. vaginalis* infection are prone to mild attacks of arthritis or suffer periodic pains in the lumbo-sacral region. Ford, in 1953, after a careful revision of the arthritis records at the Whitechapel Clinic, London, supported the view that the common form of venereal arthritis is not gonococcal. We have investigated the articular fluid of women with arthritis and vaginal trichomoniasis, but so far have not found the parasite in any case. However, the joint symptoms are cured after adequate vaginal therapy.

Several authors (Glen and Bailey, Sorel, etc.) hold the view that chronic trichomoniasis may be the cause of urethral stricture. We do not favour this hypothesis, having for many years maintained that lymphogranuloma venereum was responsible for most inflammatory fibrous strictures of the urethra.

T. vaginalis has been found in cases of acute cystitis in both men and women chronically infected by the parasite. Sometimes it has been the only possible pathogen found (Silva-Inzunza, 1950); this is more frequently the case in women. In 21 women with attacks of mild or intense dysuria, with sterile bladder urine and absence of pus cells —endometriosis excluded—we have found *T. vaginalis* in large numbers in the urinary sediment. In two cases we have found the parasite in urine obtained direct from the kidneys; both were in men with chronic pyelitis. In one of them Koch's bacillus was also found after an exhaustive investigation.

In chronic cases urethroscopy, both of the anterior and posterior urethra, shows no specific changes which permit differential diagnosis. The same can be said with regard to cystoscopy; in women a chronic inflammation of the trigone may be the outstanding feature.

Latent Infection

We classify as latent a long-standing symptomless infection in which *T. vaginalis* can be found in urethral scrapings or in the urinary sediment after urethral or prostatic massage and pus cells are present in numbers that can be regarded as pathological.

Carrier State

As with the latent case, the carrier state cannot always be clearly defined. In order to accept the existence of healthy carriers one must be certain that the parasite from the beginning caused no reaction, either microscopical or subclinical, in the host. Both latent cases and carriers sometimes produce the most violent types of infection in women.

Associated Infection

Our knowledge of this aspect is derived from the study of 1,561 cases of post-gonococcal residual urethritis, representing 25% of the patients adequately treated with penicillin. *T. vaginalis* was found in the residual secretion of 611 (39%), non-syphilitic spirochaetes in 12 (1.9%), *Staphylococcus albus haemolyticus* in 16.5%, non-haemolytic *Staph. albus* in 17.2%, *Escherichia coli* in 10.8%, and *Streptococcus faecalis* in 6.5%. Judging from the high incidence of chronic *T. vaginalis* infection found by us in males, it is probable that in a large number of cases the gonococcus–trichomonas infection was not simultaneous. In a group of patients investigated the parasite was found in the prostate in 32% of cases. Culture of the urethral secretion of 1,000 males with *T. vaginalis* infection at all stages revealed the following bacteria: haemolytic *Staph. albus*, 20%; non-haemolytic *Staph. albus*, 16%; diphtheroids and *Str. faecalis*, 5%; and *E. coli*, 3%. The remaining cultures were sterile.

Trichomonaemia

A better knowledge of *T. vaginalis* infection raises the question of the possible existence of an occasional transient trichomonaemia. During certain acute or chronic localized infections a transient bacteriaemia may be established, as in the post-operative period following prostatectomy. *T. bovis* has been cultured from the blood of infected cows, and *T. vaginalis* from the blood of infected women (Hees; Wagner and Hees). The possibility of a generalized infection in human beings would be suggested by positive serological reactions (Wendelsberger). However, haemagglutination tests for the presence of *T. vaginalis* antibodies in experimentally infected men gave negative results (Lanceley), and so far such a test has been found positive only in bulls infected with *T. foetus* presenting very severe general symptoms.

Using the fluorescein technique in fresh blood diluted with normal saline we have found free, brilliant-green, rounded bodies, as well as single, but smaller, intra-erythrocytic inclusions of the same colour, in two women with a very severe *T. vaginalis* vaginitis and cystitis with general symptoms. On several occasions we have searched for these structures in fresh blood from men and women chronically infected by the parasite, but have not found them. Our investigations of articular fluid in cases of arthritis have also been negative.

So far, evidence of trichomonaemia is not conclusive, but we believe that in certain circumstances the parasite passes into the blood stream. If such were definitely proved, the possible consequences of this passage must be carefully investigated, as the parasite may be destroyed, or live and multiply in different organs either as a saprophyte or as a pathogen. Trichomonads have been found in sections of lung tissue (Marx), in a subphrenic abscess (Navarro and De Alzaga), and in pus from an amoebic abscess of the liver (Gray and Andrews). Whether the parasites reached these unusual sites by the blood stream or otherwise is a question that must for the moment remain unanswered.

Treatment

So far there appears to be no specific treatment for *T. vaginalis* infection. A review of the literature by Bauer, of Erlangen, showed that up to 1943 nearly 100 chemical substances had been or were still being used and recommended. Since then 50 or more can be added to this list, thus signifying that none is completely satisfactory. Most drugs have been used locally, especially in women.

All chemicals so far employed are unquestionably trichomonicidal, but after cure has been achieved certain circumstances, especially in relation to sexual life, favour reinfection. With married couples, when the woman only is treated the husband remains as a permanent source of reinfection, and vice versa; prostitutes or promiscuous women and men are continuously exposed to reinfection.

Acute primary *T. vaginalis* urethritis, when treated immediately after its onset, will rapidly respond to local application of trichomonicidal drugs, such as silver salts ("argyrol," "protargol") and tincture of merthiolate.

Between 1951 and 1954 we have tried several types of treatment for acute and chronic *T. vaginalis* infection in males who were mostly (80%) between 21 and 40 years of age; only 1.7% were over 50 years. As 25% of all patients treated were married, their wives were, when possible, examined and simultaneously treated if found infected.

Treatment varies according to the clinical condition. Cases of acute uncomplicated anterior urethritis should be treated locally. The following substances have been used in urethral instillations: 5% argyrol, acriflavine (1 in 1,000), tincture of merthiolate, nitrofuran derivatives (1–2 in 10,000), and aureomycin (250 mg. in 5–10 ml. of distilled water). Previous anaesthesia of the urethra is recommended.

Patients with chronic trichomoniasis, with or without acute manifestations, should be treated both generally and locally. We have obtained the best results with injections of emetine or nitrofuran derivatives, or the oral administration of aureomycin, erythromycin, or calcium mandelate. Combinations of these drugs frequently give satisfactory results. Locally, after urethral stretching, we recommend instilling into the urethra any of the solutions recommended for the acute stage.

Medico-Social Aspects

Medico-social aspects of trichomoniasis have been little considered and often underestimated, only a few authors having drawn attention to their importance. Headache, backache, and rheumatic pains in women are a frequent cause of lack of interest or inefficiency in the home or at work. Many improve or become normal after treatment of a chronic trichomonal infection. We have also seen men suffering from intense pains in the legs, others with severe backache of neuritic type who could hardly walk, who recovered completely after adequate treatment of a chronic trichomonal prostatitis. Cases, all in men, of osteomyelitis of the spine from urinary infections have been described (Mussey). The possible route of infection is connected with the valveless system of venous channels described by Batson (1940). These channels are primarily perivertebral and have connexions with the prostatic venous plexus, veins of both bony girdles, epidural veins, and veins of the cranial cavity, as well as with the veins of the lower extremities, thoraco-abdominal wall, and head and neck. This system is connected to both venae cavae.

Invasion of the female internal genitalia may cause abortion or sterility (Rodecurt; Goodall; Cuppini). *T. vaginalis* has been found in the interior of the normal placenta, in the cut surface of the umbilical cord, and in the heart, liver, and peritoneal cavity of a foetus obtained by caesarean section. Inflammation of the Fallopian tubes may produce obstruction and subsequent sterility. Chronic inflammation of the posterior urethra, and especially of the verumontanum, may result in stricture or occlusion of the terminations of the ejaculatory ducts; epididymitis when bilateral may also cause sterility. Phagocytosis of spermatozoa by *T. vaginalis* has been observed (Kolessoff). We have not seen this phenomenon, but we have noticed that, when spermatozoa come into contact with actively motile *T. vaginalis*, many lose their tails.

Dyspareunia is frequently associated with chronic *T. vaginalis* vulvo-vaginitis; ejaculatio praecox due to a trichomonal verumontanitis is often the starting-point of impotence. Both are a frequent cause of neurosis, and many unhappy marriages can be traced back to the sexual frustration and despair engendered by these conditions.

Conclusions

Our experience indicates that *T. vaginalis* infection is a major disease problem. As in other protozoal infections of man and animals it is probably also a general disease, and this possibility needs thorough investigation. Because *T. vaginalis* infection has for so long been regarded as a local genital disease, and gynaecologists, obstetricians, urologists, and venereologists publish their findings in specialized journals, the general practitioner remains ignorant of many facts that might help him to associate significant phenomena. The time is ripe to investigate fully the problem of this infection and to emphasize its true importance.

Summary

Trichomonas vaginalis infection of the male is becoming increasingly recognized. The parasite is described and its pathogenicity and mode of spread are discussed. Infection is usually by sexual contact, but contagion

from fomites has been noted. Clinical and laboratory findings in both acute and chronic infection are described and references made to latent infection and the carrier state. The possible existence of a transient trichomonaemia is considered. Treatment of the acute stage is by urethral instillation of bactericidal drugs; chronic infection requires both general and local treatment. The medico-social aspects of trichomonal infection are discussed.

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Medical Memoranda

Huntington's Chorea in Northamptonshire

Since the report on the survey of Huntington's chorea in Northampton was published in the *British Medical Journal* of November 13, 1954 (p. 1121), a further choreic family has been ascertained in the county.

A member of the staff at the mental hospital noted that two patients with suspicious signs were related, and by tracing the family pedigree it was possible to confirm the diagnosis. At the time the survey was undertaken, therefore, (1) there were nine choreic families in the county; (2) 17 persons (not 13 as previously reported) were suffering from Huntington's chorea, giving an incidence of 6.5 cases per 100,000 of the population; and (3) 69 cases of the disease were revealed by tracing back the pedigree.

The accompanying pedigree illustrates that dyslalia presents as an early sign of the disorder, and it may be said that Huntington's chorea should always be considered in the differential diagnosis when difficulty or hesitancy of speech occurs in early adult life. The pedigree also illustrates the frequency of mistaken diagnoses of Huntington's chorea, cases having been diagnosed as general paralysis of the insane, Friedreich's ataxia, and hysteria. It is probable that the rarity ascribed to the disease is to a large extent the result of such errors in diagnosis.

In this connexion it is worth noting that some members of the family were convinced that their relatives had suffered from syphilis which had recurred as a hereditary affliction in their descendants. Rational explanation of the facts did at least relieve them of this misapprehension.

The details of the family history are as follows:

I 1.—Stated to have died in a mental hospital.

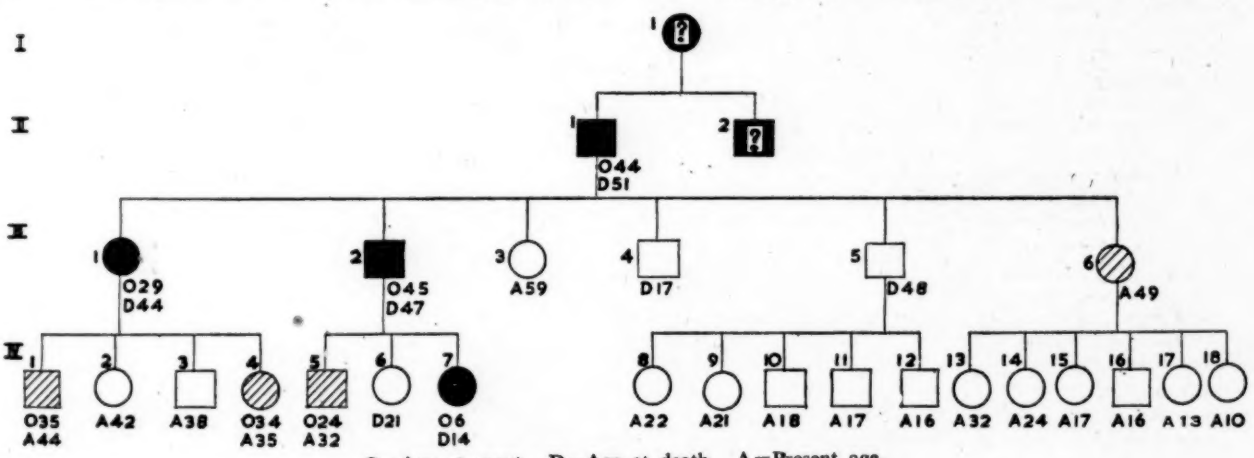
II 1.—Age of onset 44. Violent, wildly excited. Diagnosed as hereditary insanity. Choreiform movements noted when admitted to the mental hospital aged 49. Dementia with delusions of persecution; locomotor ataxia. Death aged 51.

II 2.—It is stated that he died in a mental hospital.

III 1.—Onset aged 29. Transferred from the Poor Law hospital to the mental hospital when aged 41. Demented; choreiform movements of head and hands; noisy, violent, hallucinated; ataxia. Diagnosed as G.P.I. with dementia. Death aged 44. III 2.—Onset aged 45. Threatened suicide. Admitted to the mental hospital; violent; *indistinct speech*; choreiform movements of head and eyes. Diagnosis: partial dementia, secondary to Huntington's chorea. Death aged 47. III 3.—Aged 59. No evidence of the disease. III 4.—Killed 1915, aged 17 years. III 5.—Died aged 48 following diabetic gangrene. III 6.—Age of onset not ascertained. Present age 49. Occasional involuntary movements of trunk and limbs. She is peculiar in her manner. Diagnosis: Huntington's chorea.

IV 1.—Onset aged 35. Admitted to the mental hospital aged 27. Presenting signs: *slurred speech*, ataxia, choreiform movements, dementia. Present age 44. IV 2.—No evidence of the disease. Present age 42. IV 3.—No evidence of the disease from the history. Present age 38. IV 4.—Onset aged 34. *Difficult speech*, choreiform movements. Diagnosed as hysteria in the first instance. Present age 35. IV 5.—Onset aged 24. Slow movements, change in voice, *difficult speech*, difficulty in swallowing food, all reflexes exaggerated, stiff gait, mental hallucinations. Present age 32. IV 6.—Died aged 21 in a sanatorium. She was afraid of the family affliction and, hoping to avoid it, she dieted on beans and lost weight. IV 7.—Onset aged 6 years. Attended elementary school; made little progress. Certified ineducable aged 12. Irregular movements, jerking her head, *indistinct speech*, peculiar gait, ataxia, Romberg's sign positive. Admitted to M.D. institution aged 12. Diagnosed as Friedreich's ataxia. Died aged 14. IV 13 to IV 18.—The history does not indicate that any of these persons are as yet afflicted with the disorder.

M. J. Pleydell, *M.C.*, M.D., D.P.H.,
Deputy County Medical Officer of Health, Northamptonshire.



O=Age at onset. D=Age at death. A=Present age.

Pulmonary Rheumatoid Disease

In 1948 one of us (F. D. H.) reported tentatively a possible case of rheumatoid lung disease. Although the patient was still alive and the diagnosis therefore not fully proved, it was thought worth recording in the light of the paper by Ellman and Ball (1948). This is the case referred to by Aronoff, Bywaters, and Fearnley (1955).

Case History

The patient, a male born in 1905, developed rheumatoid arthritis in 1934, relapsing in 1941 and 1947. In 1943 he noticed clubbing of his fingers, and in 1945 had a sudden attack of dyspnoea. Skiagrams of his chest were then normal. One year later pain of pleural type appeared at the right base, abating within a fortnight. Between 1928 and 1932 he had been treated for thyrotoxicosis with iodine and deep *x*-ray therapy. This condition had permanently subsided, though on examination he had marked residual exophthalmos. By 1948, in addition to signs of advanced rheumatoid arthritis, skiagrams of the lungs revealed a fine reticulation in the lower and middle zones, with coarse nodulation in the outer quadrants of the middle zones. The cardiovascular system was normal in all respects. As the appearance of the lungs did not suggest any of the usual causes of pulmonary fibrosis, and as, on the history, clubbing and radiological changes appeared during the course of active rheumatoid arthritis, we considered him a possible candidate for the diagnosis of "rheumatoid lung disease" if such a condition existed.

The later history of the case is instructive. Early in 1950 he noticed attacks of dyspnoea lasting for several minutes. These recurred on December 19, 1950, when he had a more severe attack lasting 5–10 minutes. He was admitted four days later under the care of Mr. D. Walker Ashcroft. He was extremely dyspnoeic and had marked laryngeal stridor. Laryngoscopy revealed bilateral abductor paralysis of the cords, which were pink and oedematous. A tracheostomy was performed the same day. Subsequent direct laryngoscopy, bronchoscopy, and oesophagoscopy by Mr. Ashcroft revealed no other lesion. A radioactive iodine test showed normal uptake.

Giant section of affected lung removed at necropsy. Actual size.

After this the patient lived with a permanent tracheostomy. No definite cause could be given for his abductor palsy, but it was thought possible that previous deep *x*-ray therapy to the area might have been a causative factor. In August, 1954, he died fairly suddenly at his home. In his latter months he had suffered from purpuric eruptions on the legs, and in the last fortnight from haematuria.

Necropsy was performed (D. H. M.) on August 12, 1954. Advanced rheumatoid arthritis was present. The vocal cords were fixed in the adducted position, and histology showed diffuse fibrosis in this region. Both kidneys showed chronic pyelonephritis, the right one being grossly diseased. The heart weighed 12½ oz. (354 g.) and showed slight hypertrophy and dilatation of the right side. Both lungs showed similar appearances. They were bulky and, in places, emphysematous, and showed a diffuse cystic change particularly marked in the right upper zones (see Illustration). The cysts were seldom more than 1 cm. in diameter, and there were intervening areas of relatively normal lung parenchyma. The histological changes were as follows: for the most part the cysts were lined by connective tissue which varied greatly in cellularity; in some instances the walls were made up of cellular granulation tissue containing lymphocytes, plasma cells, and cells of histiocytic type; occasionally a lining of low cubical epithelium was seen; non-cystic areas showed an increase in fibrous tissue.

These appearances were not those of the lung changes described by Ellman and Ball (1948) or by Miall *et al.* (1953), but corresponded both macroscopically and microscopically with the diffuse cystic lungs of granulomatous origin described by Cunningham and Parkinson (1950), a variety of honeycomb lung.

Comment

The cause of this type of diffuse cystic change is undecided. It has been assumed in the past that these interstitial changes are produced by added infection in congenital cystic lungs, or that the fibrosis results from diffuse interstitial pneumonia (Peirce and Dirkse, 1937). In the case here reported it is possible that the chronic laryngeal obstruction caused by abductor palsy may have played a part for some years before the obstruction became complete. Low-grade pulmonary infection may have been the sequel, the palsy being in turn the late result of deep *x*-ray therapy to the thyroid gland some years before. Cunningham and Parkinson (1950), as a result of their study of six cases, consider that these cases fall into a different group. All six cases, none of which had rheumatoid arthritis, showed a granulomatous process in the walls of the cysts and in the intercystic spaces. In the acute phase this process was characterized by a highly cellular histiocytic response, and in the chronic phase by a widespread fibrosis. In the intermediate stages foamy macrophages were present in large numbers, sometimes being the predominant cell. They suggested that the cystic spaces were not congenital but were produced by weakening of the walls of the smaller bronchioles as a result of granulomatous infiltration, the nature of which remained obscure.

This type of pulmonary change has not, to the best of our knowledge, been described in association with rheumatoid arthritis, and we therefore withdraw this case as one of pulmonary rheumatoid disease. Although these lung changes appeared during active rheumatoid disease the coincidence seems to have been fortuitous. We have seen no other similar lung changes in rheumatoid arthritis, and the literature of honeycomb lung (Oswald and Parkinson, 1949) makes no mention of rheumatoid arthritis as a coexisting disease.

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The number of patients in mental hospitals increased during 1954 by 1,352, compared with an average increase during the past five years of 1,223, according to the Annual Report of the Board of Control, 1954 (H.M.S.O., 6d.). At the end of 1954 the total number of patients under treatment for mental illness, as distinct from mental deficiency, was 152,144, of whom 140,487 were in mental hospitals. The hospitals were overcrowded to the extent of 18,932 patients. Shortage of staff was the reason for 765 beds not being in use. This is a reduction of 334 compared with the previous year, but the number out of use would be far greater were it not that many hospitals are carrying on with a smaller nursing complement than they should have. During the year the incidence of and death rate from specific illnesses again fell. The number of fresh cases of tuberculosis among patients was the lowest ever recorded, as was the death rate from the same disease. Dysentery, "once the scourge of mental hospitals," also had the lowest recorded incidence.

Reviews

HIGH BLOOD PRESSURE

High Blood Pressure. By George White Pickering, M.A., M.B., M.D., F.R.C.P. (Pp. 547+viii; illustrated. 65s.) London: J. and A. Churchill Ltd. 1955.

This work on the commonest of human afflictions is written by an expert who has spent almost a quarter of a century in its study. The book reveals at once the insight of the investigator and the erudition of the scholar. In relation to the immensity of the writing on this subject the literature reviewed (about a thousand references) is not extensive, but skilfully selected for the presentation of a modern view. The first four chapters deal with the known facts of physiological pressure regulation, but most doctors will find the section on experimental and clinical hypertension of the greatest interest, as the author's theme is based on extensive personal investigation in these fields. He gives a full account of the views of other workers, and occasionally, when these views differ from his own, we perceive him slightly on the defensive. He dislikes the generally accepted Keith–Wagener classification of retinopathy, partly because he does not accept the interpretative adjective "vasospastic," and partly because fresh exudate and old white scars are not clearly distinguished. He is a little hard-pressed in maintaining his hypothesis of an aetiological relationship between the papilloedema of malignant hypertension and elevated cerebrospinal fluid pressure, and disturbed by observations of neuro-retinopathy at moderate levels of blood pressure. Therapeutic possibilities, medical and surgical, are fully discussed, and the book ends with chapters on renal, endocrine, and obstetric varieties of hypertension.

To all physicians interested in hypertension this work will be of inestimable value. Written to stimulate, there is an honesty of outlook on what is unknown or poorly understood, and pointers to the need for further research are numerous. Some of his views are provocative: the view that hypertensives are simply at one end of a normal population distribution of blood-pressure measurements raises a philosophical dilemma on what is meant by disease. But the facts are clearly stated, and the challenge must be taken up and the idea confirmed or refuted by others. Knowledge on the subject of hypertension is on the move again, and the profession will be deeply indebted to Professor Pickering for providing such an excellent account of his well-substantiated views.

J. McMichael.

CATARACT SURGERY

Advanced Surgery of Cataract. By Daniel B. Kirby, M.D., F.A.C.S. (Pp. 271+xi; with 138 figures and 22 colour plates. £11.) Philadelphia and Montreal: J. B. Lippincott Company. London: Pitman Medical Publishing Co. Ltd. 1955.

This volume serves in a sense both as a second edition and as an appendix to the same author's monumental *Surgery of Cataract* published in 1950; it brings the advances in this important field of surgery up to date from 1949 to 1953, and reaffirms and emphasizes, and to some extent modifies, the opinions expressed on controversial matters in the initial volume. Kirby lays immense stress on the psychological preparation of the patient, his adequate sedation, thorough analgesia with topical and regional analgesics, and akinesia with curare. In the operation itself he advocates the full elevation of the corneal flap so that subsequent manipulations, such as the performance of an iridectomy and loosening of the lens, are done under full visual control, in most cases the direct rupture of the zonule fibres from the lens capsule, and post-placed direct corneo-scleral sutures of chromic catgut. Difficulties met with in the operation and subsequent complications are dealt with in detail, and the most elaborate advice is given to circumvent or to meet them.

Kirby was a surgeon who spent most of his professional life in the thoughtful study of the operation for cataract; he had acquired an experience and exercised a manipulative skill that most of his contemporaries did not possess; and, an intensely religious man, he was dogmatic in his views sometimes to the extent of fanaticism. Many of us will not agree with everything he says, and the unwary should not be unduly impressed with the conviction with which he says it; but everything he says is provocative of thought and is certainly worth study, although this ought to be critical. The writing may sometimes be repetitive almost to the point of annoyance, and the teaching is expressed with a conviction reminiscent of an evangelist rather than the detached logic usually characteristic of scientific writing, so sure was he that he was right; but the lessons are those that emerged from a lifetime of thoughtful experience and are not to be lightly discarded.

Dan Kirby died before the publication of this volume, and we are indebted to Walter Maher for seeing the work through the press. Ophthalmic surgery has been much enriched by Kirby's life work, and these two volumes will serve adequately as his memorial, reminding us in many ways of the uniqueness of his character.

Stewart Duke-Elder.

TREATMENT WITH ANTIBIOTICS

Chemotherapy with Antibiotics and Allied Drugs. Special Report Series No. 6, National Health and Medical Research Council of Australia. By Jean C. Tothurst, Glen Buckle, and Stanley W. Williams. (Pp. 106. No price.) Sydney: Australasian Medical Publishing Co. 1955.

This monograph is written by two bacteriologists and a physician on the staff of the Alfred Hospital, Melbourne, with contributions by six other authors. Its object is to provide authoritative guidance in the use of antibacterial drugs, and it succeeds in compressing within pamphlet covers all the essential information, clear and detailed instructions for treatment, and many necessary warnings against misuse. The account of the properties of different antibiotics includes a chapter on the sulphonamides. There are four chapters on the general principles of treatment, including one on synergism and antagonism, followed by accounts of the treatment of individual diseases and infections, and chapters on topical use, prophylaxis, the use of cortisone, methods of laboratory diagnosis, and sensitivity tests. It is emphasized throughout that in many infections satisfactory treatment can be based only on laboratory findings. For the initial treatment of pneumonia it is recommended that soluble penicillin be given at three-hour intervals (how often is this still done?), and it is also rightly pointed out that when streptomycin is used for an acute infection it should be given four times a day and not once as for tuberculosis. The combined treatment with streptomycin and a tetracycline advocated for brucellosis is somewhat arduous and perhaps not wholly free from risk. Intrathecal penicillin is considered necessary for pyogenic meningitis, but the use of isoniazid has removed the necessity for intrathecal streptomycin in tuberculous meningitis. There is a warning against the indiscriminate use of penicillin with streptomycin, but the authors think that to add a sulphonamide to this combination improves it for some slightly doubtful purposes. The chapter on combinations, good and bad, is in general instructive and helpful. This useful publication, although evidently intended only for Australian consumption, might well be given a wider circulation.

L. P. Garrod.

WAR SURGERY

War Surgery and Medicine. By T. Duncan M. Stout, M.B., M.S., F.R.C.S., F.R.A.C.S. Official History of New Zealand in the Second World War, 1939–45. Foreword by Major-General Sir Heneage Ogilvie, K.B.E., D.M., M.Ch., F.R.C.S. (Pp. 779+xiv; illustrated. 50s.) Wellington, New Zealand: War History Branch, Department of Internal Affairs. 1954.

Troops from New Zealand played an important part in both the first and the second world wars, and their medical services did excellent work in both. In the historical records of the war of 1914–18 no official publication dealt with clinical medicine and surgery as it affected the New

Zealand contingents. This omission has now been to a large extent remedied, for the distinguished author of this volume, who was consulting surgeon to the 2nd N.Z.E.F. in the war of 1939–45, also saw active service in the war of 1914–18, and has been able throughout the book to compare and contrast the methods adopted in both wars. Sir Heneage Ogilvie, in an introductory note, states that "the surgeons of 2nd N.Z.E.F. made a valuable contribution to the surgical potential of the Eighth Army, just as administrators and physicians helped to preserve the health of the 2nd N.Z.E.F. in the Middle East and Pacific." This book is the record of their fine work.

There are over 50 chapters of varying length dealing with every phase of medical and surgical responsibility. The contents vary greatly in importance and value. The most valuable sections deal with wound treatment, forward surgery, and shock; in this part the personal experience of the author counts for much, particularly as he makes it clear that "the consultant should be in the thick of the surgical fray." The great advance in the treatment of wounds during the latter part of the war of 1939–45 is well demonstrated. There is a valuable discussion on the treatment of wounds of the abdomen.

In the section on thoracic surgery the full statistics of wounds of the thorax give a different impression from those which give the results of operative treatment. The full statistics show how high a percentage of soldiers with thoracic wounds are brought in dead or die within a few hours of admission, a total mortality of almost 40%. This is due to the large number of wounds of the great vessels which might well be prevented by the wearing of local protective armour. The great improvement in operative results in general was of course remarkable.

The section dealing with medical diseases fully sustains the general experience that, for the first time in the history of war, malaria and dysentery were brought under control. There was only one death among 5,000 cases of dysentery admitted to hospital after the introduction of sulphaguanidine. The administrative measures for the prevention and treatment of malaria are well set out. The equivalence of "atebrin" and "mepacrine" is not clearly stated.

The volume includes an interesting survey of essential hypertension as viewed from the war-pensions aspect. Dr. Macdonald Wilson concludes, "Doctors should avoid creating invalidity and in their handling of patients be guided by the symptoms suffered rather than the high pressure recordings on the sphygmomanometer." Another significant conclusion is, "Among Service personnel there is no tendency for hypertension to occur at any earlier age than amongst the civil population." The volume is well printed on good paper and is well illustrated. It does credit both to the editor and his colleagues and to the publishers.

ZACHARY COPE.

PRIEST AND PHYSICIAN ON HOMOSEXUALITY

Homosexuality and the Western Christian Tradition. By Derrick Sherwin Bailey, Ph.D. (Pp. 181+xii. 15s.) London, New York, Toronto: Longmans, Green and Co. 1955.

Homosexuality. By D. J. West, M.B., D.P.M. Foreword by Hermann Mannheim. (Pp. 145+xiii. 15s.) London: Gerald Duckworth and Co. Ltd. 1955.

Here are two books particularly fitted to be reviewed together, for they are on the same subject, have the same aim, and are equally successful in achieving it. The first is by a member of a small informal group of Anglican clergymen that has been studying homosexuality and that published a preliminary report on it last year entitled, "The Problem of Homosexuality." The second book is by a doctor with special knowledge of psychological medicine. That a medical man should manage to write about homosexuality dispassionately and without undue bias is undoubtedly a great achievement, for letters on this subject in the medical press have not been notable for their freedom from prejudice. But that a clergyman—and a member of a morality council to boot—should be capable of writing of the "unspeakable vice" of homosexuality with such fairness, understanding, and compassion is wellnigh a miracle.

Having noted the title of the first book and the priestly qualification of its author, I confess that I opened it with reluctance, anticipating that my patience was about to be put to a severe test; but I had only to read a few pages in order to realize that what was stated on the dust-cover was actually true. The Reverend Dr. Bailey had produced not only a scholarly but an entirely fair-minded book, urging a more liberal attitude to inverts and the repeal of certain clauses in the Acts of 1861 and 1885. His book advocates also that the public should be educated to "a sense of understanding and responsibility for the men and women who labour under this peculiar handicap." Dr. Bailey confers a benefit on his own church as well as on handicapped inverts by writing such a book as this, for there can be no doubt that those of us who have long been demanding justice and sympathy for them have been inclined to attribute our failure to secure these to the blind opposition of the Church. This courageous, judicial, and scholarly history of homosexuality and the Christian tradition will do much to safeguard his Church from attacks on it by would-be reformers.

The fact that almost all the space in this joint review has been allotted to the clergyman's book does not mean that the doctor's contribution to our knowledge of homosexuality is of lesser merit, but means only that it is less surprising to find understanding on this thorny subject amongst medical men than amongst priests. Indeed, I can give no greater praise to Dr. West's excellent book than to say that it is a worthy companion volume to Dr. Bailey's more exceptional work. It is devoutly to be hoped that the attention of the members of the departmental committee which is at present discussing the problem of homosexuality has been called to two works which should be made compulsory reading for them.

KENNETH WALKER.

TEXTBOOK OF PHARMACOLOGY

Pharmacology in Medicine. A Collaborative Textbook. Edited by Victor A. Drill, Ph.D., M.D. (87 chapters+26-page index. £7 16s.) New York, Toronto, London: McGraw Hill Book Co. Inc. 1954.

This book is large in every sense. The product of the labours of eighty-one authorities, it contains a million or so words. The note on the dust cover states that it will be suitable as a book of reference for physicians as well as a students' text. The student who decided to read it all would indeed have a thirst for information and would find little time for the many other subjects of which he is supposed to have some knowledge. This work has the merits and defects of all volumes of multiple authorship, but the editor appears to have kept an unusually tight hand on his team, and the end result is remarkably uniform. The book deals with every aspect of pharmacology and its application to practical medicine. Some unusual and very good chapters deal with respiratory reflexes during anaesthesia, the role of the skeleton in pharmacological and toxicological responses, and oral and intravenous feeding. There are sections on radioactive elements, the veratrum alkaloids, and agricultural poisons. There is, in fact, almost no subject which could reasonably be included under the term pharmacology to which one will not find some reference. There is a first-class index, and each chapter is followed by a list of relevant publications mainly deriving from the United States but by no means neglecting British contributions in this field. This is an excellent book of its kind and can be strongly recommended to those who can afford its price. Some of the best chapters are on the growing points of medicine such as the steroid hormones and chemotherapy. Much of this information will inevitably require revision soon.

One is left wondering whether or not this is the correct method of exposition of so rapidly advancing a subject as applied pharmacology. It may well be that books of this type, like the dinosaurs, are the last of their kind and that the future belongs to the monograph.

E. J. WAYNE.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY OCTOBER 8 1955

SYMPATHECTOMY FOR HYPERTENSION

The last twenty years have seen many changes in the treatment of essential hypertension. Sympathectomy was given an extensive trial during the nineteen-forties, but it did not require fine statistical analysis to show that such operations were not going to cure every patient. It was evident that only some of the patients might benefit. This led to disappointment, and in some clinics to almost complete abandonment of sympathectomy. Other forms of treatment have followed with bewildering rapidity. The rice diet of Kempner[1] was tried by many with an early enthusiasm which later waned as it became evident that the treatment was less tolerable to most patients than the disease itself. The diet had an undoubted effect if adhered to, but it was difficult to prepare and was not without danger in patients with bad renal function. In the last five years many drugs have been tried. They include the methonium compounds, hydrallazine, and derivatives of the Indian plant *Rauwolfia serpentina*. The immediate effects of these on symptoms and their sometimes disadvantageous side-effects are under study, but it is as yet too early to be able to judge their effects on survival. Continuous study of patients followed for five years or so will be necessary for this, and it is to be hoped that an attempt will be made to do this in a way that will allow comparison with parallel control series. As yet no method of treatment whether by drugs or by surgery has been given a strictly controlled clinical trial.

Sufficient time has now passed for it to be possible to review the later effects of sympathectomy, and several studies have been published of groups of patients followed for five or more years after the operation. There are still no reports of studies where a parallel control series of untreated patients was available for comparison with those who were treated, and possibly there never will be. In their absence most workers have had to rely on comparison with a group of patients managed by general measures in the days before any effective drug or operation was available. The figures of N. M. Keith, H. P. Wagener, and N. W. Barker[2] are mostly used for this purpose. C. J. Longland and W. E. Gibb[3] have recently published a careful review of the results of sympathectomy in a group of 76 patients operated on in the surgical professorial unit at St. Bartholomew's Hospital. In studying survival rates, these authors classified the patients according to the state of the fundus of the eye into four grades by a system which allowed comparison with the series of Keith, Wagener, and Barker. In the group with grade-III eye changes (retinal haemorrhages and exudates) the survival rates were significantly greater in the sympathectomized patients, but the results were indeterminate in the other groups. R. H. Smithwick has reported similar findings in the past,[4 5] and H. A. Zintel and his colleagues more recently.[6] These results are open to the objection that some patients must have been rejected for sympathectomy because they were unfit for operation, whereas the medically treated group presumably consisted of all types of patient and would therefore compare unfavourably.

The effect of sympathectomy on the blood pressure of hypertensives is to produce a lasting fall in about one-fifth of the patients. K. A. Evelyn and his colleagues[7] reviewed a group of a hundred patients operated upon at the Massachusetts General Hospital. Twenty-one were found to have blood pressures which were still significantly lower than they had been at the time of operation five years earlier. Longland and Gibb found 28% of their patients to have a significant fall in pressure lasting three or more years after operation. They could, however, find no direct relationship between the fall in blood pressure and the prognosis.

The effect of sympathectomy on the symptoms of hypertension is usually good. Longland and Gibb found that symptoms were alleviated in 80% of cases, and the findings of others are in agreement. Zintel and his colleagues reported that headache was cured in 41 out of 44 in whom it had been a prominent symptom. They also found that 14 of 16 patients who had suffered from angina pectoris were relieved of symptoms by operation. The funduscopic appearances were considerably improved in the advanced cases.

Professor G. W. Pickering[8] ends his comments on sympathectomy in his recent book in these words ". . . it would seem probable that sympathectomy has a strikingly beneficial effect on a few patients, a good effect on some and perhaps no effect on others."

[1] Kempner, W., *Amer. J. Med.*, 1948, **4**, 545.
[2] Keith, N. M., Wagener, H. P., and Barker, N. W., *Amer. J. med. Sci.*, 1939, **197**, 332.
[3] Longland, C. J., and Gibb, W. E., *Brit. J. Surg.*, 1954, **41**, 382.
[4] Smithwick, R. H., *Communication to the New England Heart Association*, 1949.
[5] —— *J. Amer. med. Ass.*, 1951, **147**, 1611.
[6] Zintel, H. A., Sellers, A. M., Jeffers, W. A., Mackie, J. A., Hafkenschiel, J. H., and Lindauer, M. A., *Surg. Gynec. Obstet.*, 1955, **101**, 48.
[7] Evelyn, K. A., Alexander, F., and Cooper, S. R., *J. Amer. med. Ass.*, 1949, **140**, 592.
[8] Pickering, G. W., *High Blood Pressure*, 1955, Churchill, London.

The difficulty is in the selection, and the difficulty still exists, but Longland and Gibb give some helpful pointers. They found that operation improved the prognosis in a small group of patients with retinal and papillary oedema but without exudates or haemorrhages—a group which does not fit into any of the conventional four grades of retinal changes. Useful help may be obtained by grading the renal changes, and particularly by taking them into consideration with the funduscopic changes. Patients with increased concentrations of urea in the blood do badly, and it also seems unwise to operate on patients with marked retinal changes who also have some impairment of renal function as shown by the urea clearance test. Patients with hypertension persisting after toxaemia of pregnancy responded well to sympathectomy, as did a small group of patients in whom the hypertension was thought to be due to chronic nephritis. Like other workers Longland and Gibb found the "sodium-amytal" test useless as a prognostic aid. Pickering recommends sympathectomy when the blood pressure needs to be lowered urgently and where drug therapy is contraindicated or found to be intolerable to the patient.

The exact indications for sympathectomy are not yet crystallized, but surgeons now have more useful guides than in the past. Its place seems to lie between the extremes of wholesale employment of the early days and the more recent complete neglect accorded it by some hospital clinics, where drugs are alone used. Longer experience with drugs should clarify the positions of both forms of treatment. It may even be that a combination of the two will prove advantageous. Zintel and his colleagues found that in a few cases in which they tried the method drug therapy was more effective after sympathectomy.

LEAD POISONING IN CHILDREN

The recognition of lead poisoning as a serious industrial hazard has led to elaborate preventive measures. Even more important is prophylaxis in childhood, because the threshold for acute intoxication is low, and the greater susceptibility to lead of the developing central nervous system rapidly results in encephalopathy, often with serious mental sequelae. Danger awaits especially the young victim of pica, usually aged between 1 and 5 years, if allowed to indulge his perverted appetite on dried lead paint or plaster covering walls, furniture, or toys. Most manufacturers now ensure that toys and nursery fittings are lead-free, while domestic paint seldom contains lead, the presence of which must be labelled adequately. Outside paintwork in a dried or crumbling state may still be a menace; for instance, J. E. Bradley[1] and his colleagues found recently a raised blood level in a quarter of a group of asymptomatic Maryland children under 5 years old. In Britain lead poisoning in childhood appears to be less common than in the U.S.A.; thus J. G. Millichap *et al.*[2] could report only nineteen cases since the turn of the century, but four of their cases resulted from the unwitting application of lead-containing paint by amateur home decorators to nursery furniture within the reach of children. The danger from lead soldiers is also stressed in a recent report in this *Journal* by J. W. G. Gibb and J. F. MacMahon[3] of a child with arrested mental development from this cause. Other avoidable hazards include lead nipple shields[4–7] or ointments[8] which have affected breast-fed infants, contamination of water supply,[9] and inhalation of fumes from battery casings used as fuel.[10 11]

The protean symptoms of lead intoxication in childhood provide a diagnostic pitfall affecting almost every system in the body. An excellent clinical description is given by A. L. Tanis,[12] who found a source of lead ingestion in 85% and pica in 95% when reporting thirty-three new cases in Chicago. Initial symptoms were often non-specific, such as anorexia, weight loss, constipation, and above all vomiting, sometimes mistaken for cyclical vomiting of childhood. Classical symptoms such as lead colic or peripheral neuropathy were less common, and gingival deposits of lead sulphide were rarely seen. Striking pallor exceeded the moderate degree of accompanying anaemia. Reticulocytosis and

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[1] Bradley, J. E., Powell, A. E., Niermann, W., and McGrady, K., *Rep. Combined Meeting Amer., Canad. Paed. Soc., Brit. Paed. Ass.*, 1955, p. 57, Montreal.
[2] Millichap, J. G., Llewellyn, K. R., and Roxburgh, R. C., *Lancet*, 1952, **1**, 360.
[3] Gibb, J. W. G., and MacMahon, J. F., *British Medical Journal*, 1955, **1**, 320.
[4] Burrows, N. F. E., Rendle-Short, J., and Hanna, D., ibid., 1951, **1**, 329.
[5] Rapoport, M., and Kenney, A. S., *J. Amer. med. Ass.*, 1939, **112**, 2040.
[6] Wilcox, H. B., and Caffey, J. P., ibid., 1926, **86**, 1514.
[7] Gordon, I., and Whitehead, T. P., *Lancet*, 1949, **2**, 647.
[8] Vahlquist, B., and Sälde, H., *Acta paediat. (Stockh.)*, 1943, **31**, 180.
[9] Clark, N. S., *Arch. Dis. Childh.*, 1950, **25**, 297.
[10] Williams, H., Schulze, W. H., Rothchild, H. B., Brown, A. S., and Smith, F. R., *J. Amer. med. Ass.*, 1933, **100**, 1485.
[11] Gillet, J. A., *Lancet*, 1955, **1**, 1118.
[12] Tanis, A. L., *Amer. J. Dis. Child.*, 1955, **89**, 325.
[13] Aldren Turner, J. W., *Lancet*, 1955, **1**, 662.
[14] Mellins, R. B., and Jenkins, C. D., *J. Amer. med. Ass.*, 1955, **158**, 15.
[15] Bucy, P. C., and Buchanan, D. N., ibid., 1935, **105**, 244.
[16] Byers, R. K., and Lord, E. E., *Amer. J. Dis. Child.*, 1943, **66**, 471.
[17] Chisholm, J. J., Jr., *Rep. Combined Meet. Amer., Canad. Paed. Soc., Brit. Paed. Ass.*, 1955, p. 15, Montreal.
[18] —— Harison, H. C., Eberlein, W. R., and Harrison, H. E., *Amer. J. Dis. Child.*, 1955, **89**, 159.
[19] Caffey, J., ibid., 1938, **55**, 798.
[20] Cooper, G., *Amer. J. Roentgenol.*, 1947, **58**, 129.
[21] Schlesinger, B., Butler, N., and Black, J., *Helv. pediat. Acta*, 1952, **7**, 335.
[22] Bastrup-Madsen, P., *Lancet*, 1950, **2**, 171.
[23] Deane, G. E., Bradley, J. E., and Heldrich, F., *J. Pediat.*, 1953, **42**, 409.
[24] Ennis, J. M., and Harrison, H. E., *Pediatrics*, 1950, **5**, 853.
[25] Karpenski, F. E., Rieders, F., and Girsh, L. S., *J. Pediat.*, 1953, **42**, 687.
[26] Byers, R. K., and Maloof, C., *Amer. J. Dis. Child.*, 1954, **87**, 559.
[27] Giles, H. McC., Moore, C. J., and Still, B. M., *Lancet*, 1955, **1**, 183.
[28] Sidbury, J. B., *Amer. J. Med.*, 1955, **18**, 932.
[29] Bessman, S. P., Rubin, M., and Leikin, S., *Pediatrics*, 1954, **14**, 201.

punctate basophilia were usually present, but they may be absent in cases of very recent onset. Tremor or ataxia occurred in about a fifth, while there may be muscle weakness, due possibly to the result of direct chemical action of lead on muscle, preventing phosphocreatin resynthesis.[13] Encephalopathy occurs in about half the cases of lead poisoning in children and may be heralded by behaviour and mental disturbances, lethargy, irritability, drowsiness, or epileptiform convulsions. The cerebrospinal fluid is usually under increased pressure, and the presence of up to 100 mononuclear cells per cubic mm. may cause confusion with tuberculous meningitis[12] or viral encephalitis.[14] Death follows in about a quarter of the cases of encephalopathy, the patient usually being in status epilepticus or coma from raised intracranial pressure. Discovery of the latter condition has led to operation for cerebral tumour.[15] Focal necrosis of white matter of the brain may occur, with neurone degeneration and chromatolysis in grey matter, particularly in the basal ganglia. The danger of mental sequelae is well known. R. K. Byers and E. E. Lord[16] in Boston followed up fifty-nine survivors discharged from hospital apparently in good health. Twenty subsequently attended school, but only one child made normal progress, though the average intelligence quotient was 91. The majority showed behaviour disturbances, possessed poor reasoning powers, and lacked spatial orientation, reminiscent of the post-encephalitic state. Recent work[17] suggests that a major factor in determining permanent mental sequelae lies in recurrent exposure after an initial attack. Renal damage may also result from lead poisoning, with consequent albuminuria and glycosuria. Direct damage to the renal tubules may lead to a leak of phosphates and amino-acids in the urine[18] similar to the Fanconi–de-Toni syndrome. In these cases rickets[19] is seen instead of the lead lines which are usually such an informative sign on radiography of the long bones. It must also be borne in mind that lines of increased density may occur in other types of poisoning,[20] such as phosphorus, bismuth, and other heavy metals, and in severe infantile hypercalcaemia.[21] Laboratory confirmation of dangerous lead absorption lies in finding a blood lead concentration of above 0.06 mg. per 100 ml., while the urinary lead excretion is usually above 0.1 mg. per litre. Equally high figures may be found in cases with no overt signs of toxicity, so they should always be assessed in conjunction with the clinical picture.

Until recently the recognized treatment was vitamin D, alkalis, and a high calcium diet to promote storage of lead in the skeleton, but, even if successful in the acute stage, there was imminent danger of release of lead from the skeleton after even a transient acidosis. Dimercaprol was found to be successful in increasing urinary lead excretion in some cases,[22–24] but was not without toxic effects, occasionally even converting colic to encephalopathy. The modern agent of choice in lead encephalopathy is disodium calcium versenate (E.D.T.A.).[12 25–28] This is a chelating agent which takes up lead from blood or tissues, forming a stable compound which is biologically inactive and rapidly eliminated in the urine, in which the excretion of lead may be increased up to a hundredfold. Reported toxic effects are few, but include temporary cardiac abnormalities and urticaria. In reporting successful treatment of encephalopathy, S. P. Bessman *et al.*[29] recommend a five-day course of 0.5 g. eight-hourly intravenously, repeated after an interval of three days. Elsewhere in this issue (p. 883) Drs. A. C. Markus and A. G. Spencer report the successful treatment of three adult patients with chronic lead poisoning. The administration of E.D.T.A. resulted in the excretion of large amounts of lead, and there were no toxic effects.

In future it is to be hoped that early recognition of lead intoxication and prevention of re-exposure will prevent encephalopathy or its mental sequelae. Unfortunately there is still no single reliable screening test for lead intoxication, so a combination of pica with such varied complaints as unexplained convulsions, behaviour defect, mental retardation, abdominal pain, pallor, or irritability merits full investigation for lead poisoning.

INSIDIOUS CORONARY DISEASE

Until the aetiology of coronary atherosclerosis is better understood and prophylactic treatment possible, the keystone in the management of ischaemic heart disease rests on early and accurate diagnosis, so that treatment of myocardial infarction can be started without delay. Elsewhere in this issue Dr. Kenneth Harris (p. 874) describes the atypical manifestations of ischaemic heart disease and some of the warning signs of myocardial infarction. He emphasizes the importance of taking a very careful history, especially when dealing with classes of patients who are known to be unduly vulnerable, such as those with a family history of ischaemic heart disease or those with diabetes or hypertension. The possibility of some atypical form of anginal pain should always be borne in mind: pain in the jaw, pain in the arm, pain in the abdomen—which, to be even more confusing, may be worse after meals—are sometimes the

[1] Parkinson, J., and Bedford, D. E., *Lancet*, 1928, **1**, 4.
[2] Levine, S. A., *Medicine*, 1929, **8**, 245.
[3] Sampson, J. J., and Eliaser, M., *Amer. Heart J.*, 1937, **13**, 675.
[4] Feil, H., *Amer. J. med. Sci.*, 1937, **193**, 42.
[5] Mounsey, P., *Brit. Heart J.*, 1951, **13**, 215.
[6] Blumgart, H. L., Schlesinger, M. J., and Zoll, P. M., *J. Amer. med. Ass.*, 1941, **116**, 91.
[7] Evans, W., *Brit. Heart J.*, 1955, **17**, 15.
[8] Wood, P. H., *British Medical Journal*, 1949, **1**, 26.

sole symptoms, but almost every patient, when carefully questioned, will relate the pain to effort, emotion, or cold. Such a history calls for electrocardiographic examination. The manner in which the patient gives his history and the words he uses to describe the pains often help the physician to come to a decision whether the pain is cardiac in origin or not. In a few patients, especially in those with auricular fibrillation or hypertension, myocardial infarction may be painless, and a specially careful watch should be kept for these.

In 1928 Sir John Parkinson and D. Evan Bedford[1] were the first to observe that symptoms prodromal to myocardial infarction might sometimes be of a special type differing from classical angina pectoris, and since then other authors, including S. A. Levine,[2] J. J. Sampson and M. Eliaser,[3] H. Feil,[4] and P. Mounsey,[5] have reported similar findings. Dr. Kenneth Harris noted premonitory symptoms—usually preceding myocardial infarction by several weeks—in 23 out of 75 patients, and these symptoms he divided into three groups: angina of effort, of recent onset or with recent increase in severity; constant sternal pain, roughly simulating angina in its site and radiation; and attacks of sternal pain quite unrelated to exertion or emotion. Prodromal symptoms have an obvious importance as possible indications for prophylactic treatment to abort the impending infarction. Such symptoms, however, do not always portend a major myocardial infarct, though they show that an active pathological change is taking place in the coronary arteries or myocardium which may or may not be followed by myocardial infarction. This clinical state, intermediate between angina of effort and myocardial infarction, has been termed coronary failure by H. L. Blumgart and his colleagues.[6] W. Evans[7] has suggested that in some patients it is due to coronary arteriospasm.

The natural history of ischaemic heart disease is of a progressive process in which periods of increasing ischaemia and muscle necrosis are followed by periods of quiescence and remission of symptoms. There may be one or more major attacks of frank infarction or there may be none, in which case the whole process is gentler and the pathological picture one of widespread patchy necrosis rather than massive infarction. Any exacerbation of symptoms, or the first onset of angina of effort, whether or not it heralds impending myocardial infarction, is an indication that the disease is progressing. Hence there is much to be said for treating all such patients with a period of rest and possibly anticoagulant therapy in selected cases, as suggested by Paul Wood,[8] until the active pathological process has subsided and symptoms have regressed.

HYDROCORTISONE IN ANOGENITAL PRURITUS

All considered pronouncements on the subject of pruritus emphasize the importance of diagnosis and of complete diagnosis. This is particularly true of pruritus of the anogenital region, though it is perhaps more satisfactory to deal with the problems separately as anal and genital pruritus, for different considerations are apt to arise.

Anal pruritus is more common in the male; it may be the only disorder in that particular patient over the course of many years. It is nevertheless important to consider the whole patient and to give attention to local factors. Psychological and particularly sexual maladjustments are likely to play a part. Locally, threadworms, to which attention was drawn by W. P. MacArthur,[1] and ringworm infections may escape notice. To exclude ringworm, mycological examination and inspection of the toes are necessary. Pruritus ani, with or without monilial infection, is an increasingly frequent consequence of antibiotic treatment. Sometimes, but not always, treatment of a general or local disorder will cure the pruritus. In many patients, however, whether or not an exciting cause is found, pruritus ani will persist and the habit of itching and scratching will establish a vicious circle. The older surgical approach to the problem is less common to-day, though the distress occasioned by the malady is sometimes extreme. Superficial *x*-ray therapy and Grenz-ray therapy, administered with care in a general scheme of treatment, can help. Infection may have an important secondary role; gentian violet may then give benefit, and, because moistness of the parts is common and increases itching, a tragacanth emulsion of aluminium hydroxide and glycerin is useful. The debilitating and sensitizing effects of anaesthetic and antihistamine applications contraindicate their use, and in general the simpler remedies are the more effective. Recently Brian Russell,[2] R. Turell,[3] and others have drawn attention to the value of hydrocortisone ointment, and most dermatologists have found it beneficial. It does not cause sensitization or any other side effects, relief is often immediate, and very little need be applied. While it is of value in treating genital pruritus in the male, the problem here is more often part of an eczema or neurodermatitis.

In the female, vulval pruritus calls for a rather different approach. Emotional considerations are important, as is the susceptibility of the parts to hormonal and other general influences. Local factors are much more significant than in anal pruritus and necessitate the most careful examination and investigation. Glycosuria as a possible cause cannot always be dismissed by a single examination of urine. Infection, bacterial or monilial, may not be evident because of its location high in the vagina, perhaps following the use of internal tampons. Slight changes in the vulval skin, especially atrophic changes, may be associated with intense pruritus and may be apparent only on careful inspection. These and other factors may lead to malignant or premalignant changes, when surgery is the proper line of approach. In all patients with pruritus in the anogenital region the fear of cancer, or less often the fear of venereal disease, may have some bearing on symptoms. These are some of the reasons for considering anal and vulval pruritus separately, though occasionally the one may start the other.

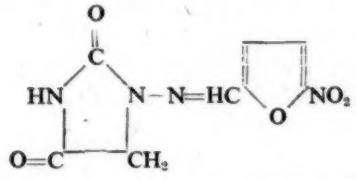
Turell found hydrocortisone creams of greater benefit than lotion. He arbitrarily classifies anogenital pruritus

[1] MacArthur, W. P., *Practitioner*, 1945, **154**, 266.
[2] Russell, Brian, *et al.*, *Lancet*, 1955, **1**, 1038.
[3] Turell, R., *J. Amer. med. Ass.*, 1955, **158**, 173.

into eight different categories and indicates the merits of this treatment in each, but this is perhaps less profitable than it seems. He found no particular advantage in fluorohydrocortisone over hydrocortisone. Brian Russell's investigations were elaborately controlled, and he concludes that hydrocortisone ointment is of significant value, particularly in anogenital pruritus and otitis externa. Only one patient of 131 was sensitive to the application, and that was due to the base. Hydrocortisone offers an advance in local therapy which has in the past ranged, with limited satisfaction, from the injection of anaesthetics in oil to the local application of honey or insulin. It is important to remember that it is only a local measure giving symptomatic relief. The absence of side effects is welcome, and though relapses may follow withdrawal relief helps to break a habit, gives the patient confidence, and affords an opportunity to rest and regain health.

NITROFURANTOIN

Several reports have appeared recently of a new drug which promises to be of benefit, especially in the treatment of urinary infections.[1-3] The drug is N-(5 nitro-2-furfurylidene)-l-aminohydantoin, and its trade name is "furadantin." The drug is chemically synthesized and its formula is illustrated below:



It is soluble at body temperature and at the *p*H of acid urine to the extent of about 0.2 mg. per ml., and it readily forms stable supersaturated solutions, so that concentrations up to 0.4 mg./ml. may be obtained in the urine. When doses of 5 to 10 mg./kg. body weight are given the drug appears in the urine in half an hour. About 40% of the oral dose is excreted in the urine; most of the remainder is excreted as inactive substances that may colour the urine brown. Toxic effects so far reported in man have been trivial, but must be carefully looked for in view of the chemical formula of the drug.

B. A. Waisbren and W. Crowley[4] have now reported the results of further laboratory and clinical studies with nitrofurantoin. They confirm the wide antibacterial activity of the drug, whose spectrum is like that of chloramphenicol, and show that against some strains of *Bacterium coli* it is rapidly bactericidal. The drug was found in the laboratory to be particularly effective against *Staphylococcus pyogenes* and *Proteus* (though it is not stated whether these organisms were actually killed or only suppressed). It was ineffective against *Pseudomonas*. Waisbren and Crowley also report clinical results in 60 patients with urinary tract infections treated with nitrofurantoin. They conclude that results were satisfactory in 27 cases, unsatisfactory in 12, and indeterminate in 21. There is a suggestion that the drug was most effective against *Proteus* infections, and that it was more active against some of the *Pseudomonas* infections than might have been expected from the results of *in vitro* sensitivity. But, as the authors point out, results of treatment in chronic urinary infections are hard to assess, and they cautiously conclude that the results were about as good as would have been expected with any other single drug. Nitrofurantoin sometimes appeared to be successful after other drugs had failed, and drug resistance did not seem to be a serious problem. S. J. Heffernan, P. W. Kippax, and W. A. V. Pamplin[5] in a report of clinical and bacteriological studies on cases of *Proteus* bacilluria claimed improvement in eleven out of twelve cases treated for five days, whereas out of five control patients observed over the same period none showed any improvement. Clearly the drug has great possibilities, and, if its relative lack of toxicity is confirmed, it would seem to be worthy of extended trial, especially in urinary infections, as a single drug and perhaps also in combination with other drugs.

[1] Norfleet, C. M., jun., *et al.*, paper read before Annual meeting South-eastern section, Amer. Urol. Ass., Boca Raton., Fla., U.S.A., 1952, 26.
[2] Mintzer, S., *et al.*, *Antibiot. and Chemother.*, 1953, **3**, 151.
[3] Schatten, W. E., and Persky, L., *Amer. J. Surg.*, 1953, **86**, 720.
[4] Waisbren, B. A., and Crowley, W., *Arch. intern. Med.*, 1955, **95**, 653.
[5] Heffernan, S. J., *et al.*, *J. clin. Path.*, 1955, **8**, 1123.

X RAYS IN THE FIELD

Recently it was announced in Washington by the Army Surgeon-General's Liaison Office that a newly designed portable *x*-ray unit would soon become available. The new equipment is intended for use on the battlefield to *x*-ray wounded soldiers, and it can produce a radiograph without electricity, water, or darkroom. The complete unit weighs only 22 lb. (10 kg.) and may be carried on the back of a medical aid man. The source of radiation in this apparatus is a small piece of radioactive thulium, which emits gamma-rays as effective as *x* rays emitted from a high-voltage diagnostic set. The element thulium is a rare earth of the lanthanide series and it is made radioactive by neutron irradiation in an atomic pile. The activity produced in the thulium has a half-life of 129 days, and consequently the source must be rejuvenated in the atomic pile about every eight months. When the source is not in use it is stored in a lead pot with 2-in. (5-cm.) thick walls to protect the operator from radiation.

The radiographs are recorded on radiosensitive paper instead of film. The paper is carried in a special light-tight and waterproof cassette. The cassette also contains pads saturated with developer and fixer which are separated from each other and the film by leak-proof dividers. After the paper is exposed the dividers are withdrawn in turn and the radiograph is recorded. Radiographs produced in this way are reported to lack the fine detail of standard *x*-ray films, but they are suitable for use in the field and in emergency. Exposures are timed with a wrist-watch, and in comparison with a normal *x*-ray set the exposure times with the thulium source may be rather long. In Britain the strength of readily available material is such that the exposure times would be measured in minutes rather than seconds. No information about the source strength in the American set is given. The apparatus is reported to be simple

and easy to handle and operators can be trained in a few hours. More development work is planned before the apparatus can be standardized for commercial manufacture.

In any future war a serious limitation on the usefulness of mobile field equipment using radiosensitive film or paper may prove to be the high radiation levels likely to occur over considerable areas owing to explosions of nuclear weapons. All radiation reaching the sensitive films or papers causes blackening; hence they may be completely fogged by exposure to radiations from the explosive centre of the weapon or the subsequent radioactive fall-out before they can be used. It would appear that the techniques of xero-radiography offer a satisfactory solution to this problem; the radiosensitive surface may be freshly produced just before the exposure is made, so that the operator can avoid the fogging due to the general background of radiation.

MUSCULAR CIRRHOSIS OF THE LUNGS

In chronic inflammatory diseases leading to disorganization and destruction of lung substance the histological picture often shows a predominance of smooth-muscle fibres. In such cases, however, it is doubtful if there is any real increase in muscle tissue, the muscle fibres being derived from the blood vessels and bronchioles, where they normally abound. Thus, some care is required in interpreting the apparent increase in muscle in diseased lungs. L. Rubenstein, W. H. Gutstein, and H. Lepow have recently drawn attention to a rare pulmonary disorder in which there is a diffuse proliferation of muscle tissue throughout both lungs.[1] This condition, which the authors describe as "pulmonary muscular hyperplasia," has been reported in medical literature from time to time since 1872, when it was first described by von Buhl under the title of "muscular cirrhosis of the lung."[2] Although the aetiology of the disease is not always certain, enough cases have now been described for a clear picture of the morbid anatomy and the clinical signs of the disorder to be drawn. The victims, usually adults, suffer from progressive dyspnoea culminating in right heart failure; the relentless course of the disease is often hastened by attacks of acute dyspnoea caused by spontaneous pneumothorax. At necropsy the lungs are remarkably firm, with a dense stroma of fibrous and muscular tissue, and have a honeycomb appearance due to diffuse cystic or bullous changes.

The first clue to the aetiology of this curious pathological process appeared when G. Berg and G. Vejlens[3] described a case in which histological examination of the brain established beyond doubt the diagnosis of tuberous sclerosis, a disease usually manifested by neurological disturbances leading to fits and mental deterioration. Subsequent reports from the European continent[4–6] and from Britain[7] confirmed that the lungs are sometimes involved in the complicated mesodermal dysplasia of tuberous sclerosis, and it has been suggested that in some cases the pathological process is confined to the lungs. Some support for this hypothesis was adduced by J. Dawson,[8] who, in a comprehensive review of the subject, described four patients with pulmonary tuberous sclerosis. Dawson showed that, though most patients with tuberous sclerosis seek medical advice for mental symptoms or for skin eruptions, those patients having pulmonary lesions present with respiratory symptoms. In such cases the other stigmata of tuberous sclerosis may not be obvious. Thus there is an inverse relationship between the severity of the neurological and of the pulmonary disturbances. Certainly a full histological search should be made for other evidence of tuberous sclerosis in these rare cases of diffuse pulmonary hyperplasia.

[1] Rubenstein, L., *et al.*, *Ann. intern. Med.*, 1955, **42**, 36.
[2] Von Buhl, L., *Lungenentzündung, Tuberculose und Schwindsacht*, 1872, Munich.
[3] Berg, G., and Vejlens, G., *Acta paediat.* (*Uppsala*), 1939, **26**, 16.
[4] —— and Nordenskjold, A., *Acta med. scand.*, 1946, **125**, 428.
[5] Samuelsen, E., *Acta radiol.* (*Stockh.*), 1942, **23**, 373.
[6] Paliard *et al.*, *Poumon*, 1946, **2**, 205.
[7] Oswald, N., and Parkinson, T., *Quart. J. Med.*, 1949, **18**, 1.
[8] Dawson, J., *Quart J. Med.*, 1954, **23**, 113.

THE ELECTRON MICROSCOPE

Five years ago the electron microscope was still very much a tool for the specialized research laboratory.[1] The limitations of specimen thickness and the need for pure specimens of protein, viruses, or even bacteria entailed complex and skilled preparative techniques. In the intervening years this situation has changed through the development of methods for cutting ultrathin sections for electron microscopy. This began with Pease and Baker's modification of a standard microtome which enabled sections to be cut about ten times thinner than those used in normal histological practice. Since then new microtomes have been developed, the majority of which use the thermal expansion of a metal rod to give the very small movements required to advance a block by the requisite 10 mμ for each cut. New and more precise techniques for the fixation and embedding of tissues have been evolved and much work has been done on the development of suitable cutting edges. Specially polished steel, glass, and diamond knives are being successfully used in current practice. As a result of all this new work an increasing number of studies on the fine structure of cells and tissues are being reported, and histologists already have a more detailed knowledge of the structure of, for example, cell mitochondria than they had fifteen years ago of the intimate structure of whole cells. The gain in detailed knowledge of cell structure which this represents can be appreciated from the fact that with the light microscope the mitochondria themselves—each occupying about one ten-thousandth part of the volume of the average cell—were the smallest particles recognizable as structural entities in cells. The new histology which is developing takes us much nearer to the dimensions of the ultimate building-bricks of biological structures—the component protein, carbohydrate, and lipid molecules. And an unfamiliar terminology denoting new structural entities—for instance, cristae mitochondriales, endoplasmic reticulum—is now taking its place beside the classical terminology of nucleus, nucleolus, and cytoplasm.

[1] *British Medical Journal*, 1950, **2**, 1432.

EMERGENCIES IN GENERAL PRACTICE

THE ACUTE ABDOMEN IN CHILDREN

BY

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There can be few doctors who have never missed an acute abdomen. In England and Wales from 1949 to 1953, 936 children died from appendicitis, 561 from intussusception, and 721 from other forms of intestinal obstruction. It is this background of possible catastrophe which makes every child with abdominal pain such an urgent and worrying problem. Yet the solution is by no means easy; it asks from the family doctor the prompt recognition of the acute abdomen amid the profusion of intestinal upsets which are his everyday responsibility, and from the hospital close collaboration between surgeons and paediatricians and a sufficient flow of cases to ensure that effective therapeutic skills are maintained.

It is not unfair to say that with earlier recognition, effective pre-operative resuscitation, experienced surgery, an adequate supply of fluid and electrolytes in the period immediately following operation, and the proper use of antibiotics the majority of the deaths listed above would have been avoided. The general principles which should govern our approach to the acute abdomen have already been presented in the two previous articles by Professor Milnes Walker.* We shall describe here the clinical features which are of special importance in children, and which make it possible in most cases to recognize the "surgical" emergency and at the same time to distinguish a number of "medical" conditions which may resemble it very closely. We shall also indicate, where we can, the time limits within which diagnosis should be reached and treatment started if a further reduction is to be achieved not only in deaths but also in distressing illness and the length of stay in hospital.

Symptomatology in Children

It is more important for the family doctor to suspect quickly the presence of an "acute abdomen" rather than to be correct with the final diagnostic label. The main task is to decide from the history the relationship and relative importance of pain, vomiting, fever, and alterations in bowel behaviour, and then by patient examination to assess the significance of posture and appearance, tachycardia, tenderness, increase in muscle tone, and abdominal distension. We set great store on a detailed account of the illness, taken from the person who has been in closest contact with the child, and we know that a second or even third examination after a short interval may be necessary before the physical signs can be properly assessed.

Pain.—The first essential in listening to the history is to try to decide whether the pain is continuous or intermittent, a continuous ache or an intermittent colic. For example, although in appendicitis there may be colicky exacerbations there is almost always a background of *continuous* pain, whereas the pain of acute mesenteric adenitis is *intermittent* in character. Again, appendicular pain is less severe than the violent colic of intussusception, urinary tract obstruction, and the sharper examples of mesenteric adenitis. We must avoid being lulled into the false security of interpreting a mild continuous pain as a pain of no importance.

Vomiting is a common symptom. In both appendicitis and intussusception it may occur before the pain. The frequency and amount will vary in different children in what appear to be similar conditions, but where it is copious and persistent the probability of intestinal obstruction should come quickly to mind. In a minority of children with appendicitis and intussusception vomiting will be absent.

Fever is often present and its interpretation can be difficult. It generally occurs quite early in intussusception and is of no help in separating this from gastro-enteritis. It is usually higher in acute pyelonephritis and pneumonia than in appendicitis, but a high temperature does not exclude the latter. This is particularly the case where acute appendicitis is associated with tonsillitis or pharyngitis, or where peritonitis has already developed. Fever with peritoneal infection tends to be higher in children than adults.

Alteration in Bowel Behaviour.—This varies a good deal within the different conditions and there are many pitfalls. A newborn infant with duodenal atresia can still pass meconium. An infant with acute intussusception is rarely constipated, and many such children pass one or two apparently normal stools on the first day. Although it is unusual for an infant with acute intussusception to have more than two stools in each 24 hours, an important minority pass frequent small brown stools and are watched and treated as cases of bowel infection. Constipation, though common in appendicitis, is by no means the rule. Absolute constipation, especially with persistent vomiting, is very suggestive of complete intestinal obstruction. Where diarrhoea is the most striking feature of the illness we should think first of dysentery or gastro-enteritis, yet in our experience as many as one in eight children with appendicitis may have diarrhoea before operation.

Physical Findings

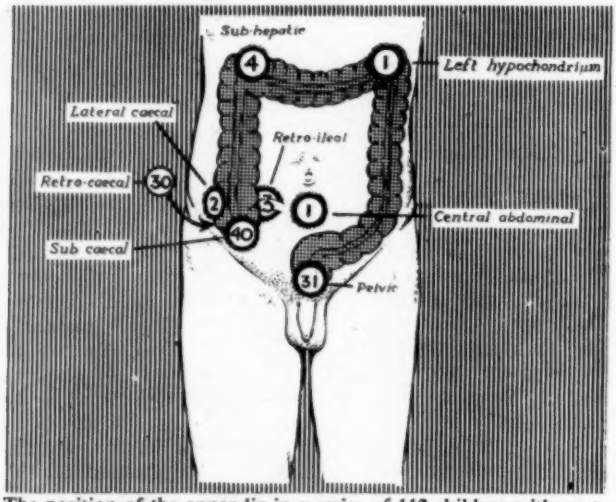
Tenderness.—If pain is the primary symptom, tenderness is the most important sign of an acute abdomen. It is assessed by noting whether the child consistently winces or attempts to pull away the palpating hand when gentle pressure is applied to a particular spot. In young children it is better not to ask whether a particular area is sore, as the reply is often misleading. In appendicitis localized tenderness is the most useful early sign, and for diagnosis within the first 24 hours it is dangerous to wait until guarding is added to it. The point of maximum tenderness varies more in the child than in the adult. The sites where it may be found in the first 24 hours are shown in the diagram on the next page.

Though the suspicion of intussusception should rest essentially upon the history and never be delayed in the home until the tumour is felt, in over half the affected children the tumour will be tender. Tenderness in mesenteric adenitis is less severe and more diffuse than in unperforated appendicitis, and though present in the right iliac fossa it may extend upwards and to the left, towards and

*See *British Medical Journal*, September 24 (p. 782) and October 1 (p. 842).

sometimes beyond the mid-epigastrium. The tenderness of pyelonephritis, hydronephrosis, or pyonephrosis is generally in the flank or loin, though in a large hydronephrosis it may be most evident in the upper abdomen.

Posture.—The natural position adopted by the child with an acute abdomen is a most valuable sign. The near stillness of appendicitis, at least during the day, contrasts strongly with the intermittent spasms of intussusception, the restlessness of mesenteric adenitis, and the rolling about of severe renal colic. Parents can generally give an accurate account of the child's behaviour in this sense, and it is important to ask for it.



The position of the appendix in a series of 112 children with acute appendicitis. The circles indicate the point where localized tenderness would have been obtainable in the first 24 hours.

Facial Appearance.—Pallor following a severe spasm and the return of normal colour in the interval is characteristic of early intussusception. With the intermittent colics of mesenteric adenitis and urinary tract obstruction the child may be flushed throughout, or flushing may give place to pallor, depending on the severity of the attack. Many children with acute appendicitis have a cherry-red flush, sometimes with a faint trace of blue, and a circumoral pallor. Evident cyanosis usually means pneumonia, generalized peritonitis, or prolonged intestinal obstruction.

Tachycardia is the rule in appendicitis, intussusception, and other forms of established intestinal obstruction. Sometimes, however, the pulse will be scarcely raised in appendicitis, and if the child is seen between the colicky episodes of mesenteric adenitis or renal colic it can also be normal.

Involuntary Guarding.—This is a difficult sign to assess in the early stages, and it is essential to start with very light palpation away from the site of the suspected lesion. In most cases of appendicitis the increase in muscle tone will first be felt in the lower right rectus. The abdomen of the apprehensive child may at first appear rigid all over, but with a warm hand and slowly increasing pressure the muscles will relax unless increase in tone is present. It is also common to meet lower abdominal or even more widespread guarding on first examining the child with mesenteric adenitis, only to find the muscles relax as the child is involved in conversation while steady pressure is maintained.

Abdominal Distension.—Abdominal distension in a child with an acute abdomen means in most cases progressive intestinal obstruction or spreading peritonitis. It may, however, be present with acute pneumonia, and we have sometimes seen it in severe examples of mesenteric adenitis and with renal colic.

Acute Appendicitis

In most affected children the attack is the first of its kind, though as many as one child in four may have had one or two attacks of abdominal pain in the previous year. Pain is the main symptom, and it is continuous. Though colicky exacerbations occur, the pain is generally less severe than in intussusception, mesenteric adenitis, and renal colic. A history of pain starting in the centre of the abdomen and then moving to the right iliac fossa is less common in children than in adults. The pain will often start and remain, unless perforation occurs, in any of the varied sites shown in the diagram. Vomiting occurs in nine out of ten children at some stage of the illness, and in some it will be the presenting feature. Diarrhoea is present in up to 12% of children when the appendix is situated behind the lower ileum or in the pelvis. The child lies still, on his back or right side, with his thighs flexed. He generally resents being asked to move. His facial appearance has already been described. The tongue has a fine white coating or fur, and oral fetor is generally present. The abdomen is not distended, but the lower half may move poorly with respiration. Persistent localized tenderness over one of the sites shown in the diagram, with or without involuntary guarding, is the diagnostic sign. Rectal examination is resented by the younger child and interpretation of the response is often difficult. If the diagnosis is clear without it, then it should be omitted, but if there is any doubt it should be carried out, since it may reveal an unsuspected pelvic appendicitis.

It is particularly important to remember that appendicitis does occur in young children. The picture under 3 has been vividly and accurately described by Williams.* The initial features are often deceptively general, with peevishness, irritability, feverishness, refusal of food and vomiting. What is more, the pain often seems less acute in these children, though they will say their tummy is sore and the mother generally recognizes that they are in pain. Vomiting is an almost constant symptom, and is often early and frequent. Diarrhoea also is more common than in older children, and this, with the milder pain, often leads to a delaying diagnosis of intestinal upset or infection. Yet at this age the tendency to early perforation and the development of peritonitis is greatest.

At all ages, any abdominal pain that has continued without intermission for several hours, especially if associated with vomiting, should be regarded as acute appendicitis, and expert assessment should be made at home or in the hospital as soon as possible.

Acute Non-Specific Mesenteric Lymphadenitis

This is the condition most commonly mistaken for appendicitis, and it is much more frequent. We believe that careful clinical attention is sufficient in most cases to establish the difference and so spare the child an unnecessary laparotomy. Our experience confirms in almost every detail the clear account given by Aird.† The presenting symptom is pain. This is generally central in position, but, unlike appendicitis, it is intermittent in character. Each attack rarely lasts more than 10 to 15 minutes, but some may be of great severity. In the intervals the child is entirely free from pain and much more active than any child with true appendicitis. Many of these children have had more than one previous attack of a similar kind. The child is often active in the intervals, though "twisty" and crying when the pain comes on. Vomiting will occur in a severe attack, but is less common than with appendicitis. Diarrhoea practically never occurs. Many of the children will have a history or evidence of recent pharyngitis. A clean tongue is the rule unless there is pharyngeal infection or repeated vomiting. Tenderness is less local than in appendicitis, and may spread upwards towards the epigastrium. With gentle but prolonged palpation the initial voluntary guarding will go and it is possible to feel the posterior abdominal wall in a way that would be impossible in appendicitis. The glands themselves may be felt. Mesenteric adenitis is a self-limiting though sometimes protracted disease with relapses and remissions over many months.

*Williams, H., *British Medical Journal*, 1947, **2**, 730.
†Aird, I., ibid., 1945, **2**, 680.

There is no specific treatment or any evidence that appendicectomy shortens the course of the disease. Where genuine doubt exists laparotomy should be carried out, for it is wiser to be on the safe side.

Intussusception

Intussusception mainly affects children from the second to the eighteenth month of life. The onset is sudden and the mother can often give the exact time when the initial pain or vomiting began. The pain is intermittent, is generally severe, and may be followed by pallor and collapse. Not all infants, however, respond to pain in the same way; some scream and draw up their knees, others cry loudly, others whimper and whine, while a few may be intermittently restless. The spasms may recur every few minutes, or at intervals of an hour or more. Vomiting is almost always present in the first 24 hours, and is often the presenting symptom. One or two normal stools may be passed after the onset, but increased frequency of the motions and true diarrhoea are uncommon. When blood is passed spontaneously from the rectum in association with the above picture the diagnosis is almost certain, but in nearly half the children blood is absent on that vital first day. Fever is often present, even in the first 24 hours, and is not a pointer in itself to intestinal infection. The ability to feel the tumour requires constant practice and often sedation of the child. A strong suspicion of intussusception can be obtained from the history, and delay for repeated abdominal palpation in the home is not justified. Any previously healthy child, especially between 2 months and 2 years of age, who is suddenly seized with sharp intermittent abdominal pain and vomiting, should be regarded as suffering from intussusception and sent to hospital without delay.

Acute Intestinal Obstruction

In children, acute intestinal obstruction of varied origin is much less common than the conditions already considered; but acute obstruction carries a high mortality. It can best be considered in two age groups—newborn infants and older children. In the latter the traditional features of intermittent colicky pain, copious vomiting, and complete constipation will be present, and careful examination of the abdomen in a good light will often show early distension, palpable coils of distended gut, and even visible peristalsis. On auscultation vigorous bowel sounds are heard, in contrast to the virtual silence of a spreading peritonitis.

In the first week of life vomiting, not pain, is the main feature of intestinal obstruction. The vomiting generally begins on the first or second day and is persistent. If the vomit is golden yellow or green in colour, the presence of a duodenal atresia is almost certain. It is important to remember that such children can pass meconium and that distension affects at first only the upper abdomen, so that it is readily missed. With lower intestinal atresia, malrotation of the gut, and volvulus the vomiting may develop more gradually, but it is progressive and associated with obvious distension. Intestinal obstruction in the newborn is still associated with mortality rates between 25% and 50%. It is an excellent example of the need for early recognition, effective fluid and nutritional control, and specially experienced surgery. Early recognition will be achieved only if every genuinely vomiting infant in the first week of life is examined with intestinal obstruction in mind.

Differential Diagnosis in Children

This is a big subject, and it is possible to draw attention to only the more important points. Faced with probable appendicitis, the practitioner must first consider the possibility of urinary tract infection, pneumonia, and infective hepatitis. If urinary tract infection is imitating an acute abdomen the fever will be over 102° F. (38.9° C.), there may have been an early shivering attack, and the child will be flushed and ill. In the older child there will be frequency of micturition and dysuria, but these are often absent in younger children, and the true explanation is revealed only by the discovery of pyuria, which may necessitate the examination of several specimens of urine before the pus is found. The pain in pyelonephritis is generally continuous. With an infected hydronephrosis there may also be phases of colic. Should the latter be on the right side it can resemble retrocaecal appendicitis. There may have been several previous episodes of abdominal pain, one at least of which will have been a severe colic and have lasted more than an hour. We have also been impressed with the number of children in whom the early pain of hydronephrosis has lacked any reference to the urinary tract and has been situated in the centre of the abdomen. A helpful point is that the child, when asked to indicate where the pain is, may give the "kidney sign," grasping the affected loin with his thumb behind and his fingers in front.

In acute pneumonia the child will be restless, with high fever and rapid respirations, nostril movements, and possibly cyanosis, and there may or may not be obvious physical signs over the affected lung when the child is first seen. A preceding history of coryza or bronchitis in the child or other members of the family will help. Shivering and delirium, which may be present in pneumonia, are almost unknown in appendicitis. At first sight pneumonia may be difficult to distinguish from established peritonitis with grunting respirations and early circulatory failure; but the length of history and the abdominal signs in the child with peritonitis should be sufficient to decide between the two conditions.

In infective hepatitis anorexia is generally an early and striking symptom: vomiting tends to be more in evidence than pain, and the latter is intermittent, usually in the upper abdomen, and is often associated with an enlarged and tender liver. Bradycardia when present is suggestive, but until jaundice appears in the patient or bile in the urine the distinction from subhepatic appendicitis may be difficult.

The most likely alternatives to possible intussusception in an infant are acute otitis media and meningitis. Severe pain at this age, whatever the site, tends to produce a similar general reaction, though the pallor and collapse which follow a severe spasm in intussusception are not found in otitis media and are rare in meningitis unless the child has had a fit. With a febrile, vomiting infant, crying, or in obvious pain, it is particularly important to examine the ears for otitis media and to look for that drowsy irritability, fullness of the fontanelle, and moderate neck stiffness which would point to meningitis. In older children with suspected intussusception Schönlein–Henoch syndrome (anaphylactoid purpura) must be remembered; here, unless the characteristic urticario-purpuric rash is present on the elbows, legs, and buttocks, the distinction may be difficult. In between the severe spasms of pain in this condition the abdomen is often free from tenderness and no tumour can be felt. Examination of the urine may reveal an associated haematuria.

The special features of obstructed and strangulated hernia and of torsion of the testis, the appendix testis, or Meckel's diverticulum will not be described here. It is wise to keep somewhere in mind that abdominal pain, vomiting, a bluish-red flush to the face, and furring of the tongue may indicate not acute appendicitis but diabetic ketosis. Except in children with Hirschsprung's disease, we have never seen constipation present as an acute abdomen, although such cases are sometimes referred to hospital as suspected acute appendicitis.

Management

The essential contribution of the family doctor to the management of the acute abdomen is its early recognition. In acute intussusception this means recognition or a shrewd suspicion and reference to hospital within 24 hours of the first symptom. It is important not to wait for the passage of blood or feeling the tumour.

In 40% of the children sent to the Royal Victoria Infirmary, Newcastle-upon-Tyne, with appendicitis in the last three years the appendix had perforated on admission. This rarely happens in the first 24 hours. Here again the aim should be diagnosis and treatment on the first day of the disease. In appendicitis, however, the responsibility for the delay in recognition rests largely with the parents. The family doctor has therefore the additional task of helping the parents in his practice and community to realize that abdominal pain in childhood should always be taken seriously. Whenever it has continued for several hours without interruption medical advice must be sought. The practitioner must also remind himself sometimes, and warn his patients always, that purgatives should never be given to a child with abdominal pain. Sedatives and analgesics, especially morphine, should be avoided in intussusception and appendicitis; and, even where peritonitis is suspected, it is wise not to start antibiotics at home.

Abdominal pain associated with vomiting and abdominal distension is an urgent call for admission to hospital, but when a confident diagnosis of mesenteric adenitis has been made the child can be cared for at home. If there is any doubt, the child should be seen at home or in the hospital by an experienced consultant, and in the latter case if the diagnosis is confirmed the child can return home under the care of the family doctor. The treatment is simply rest in bed, with aspirin, 1 gr. (65 mg.) per year of age two or three times a day, to relieve pain, and procaine penicillin, 300,000 units daily, only if the temperature is over 100° F. (37.8° C.) and a substantial tonsillitis is present. A single episode does not usually last more than a week to ten days.

Aspirin or codeine are not sufficient to relieve the pain of renal colic, and "nepenthe," one minim (0.06 ml.) per year of age three or four times in the 24 hours, should be used. There is, if required, a preparation of nepenthe suitable for injection. An acute urinary tract infection detected within the first week will generally respond to a sulphonamide alone. We use sulphadimidine in a dosage of 0.1 g. per pound (0.45 kg.) of body weight per day for eight days. Sulphonamide preparations containing sulphamerazine should be avoided owing to the risk of renal damage with haematuria. If, however, the attack is an intensification of a more long-standing infection, then admission to hospital is essential so that the organism can be isolated, the right antibiotic used, and the presence or absence of anatomical abnormalities in the urinary tract determined. A chronic urinary tract infection is a serious condition calling for persistent treatment, often for several months. Consideration of the treatment of pneumonia, meningitis, infective hepatitis, and other conditions which may imitate the acute abdomen would be out of place here. In any child with abdominal pain the urine should always be examined for pus, red cells, bile, and sugar.

The acute abdomen will always remain a serious and difficult professional responsibility, but attention to the character of the abdominal pain and the behaviour of the child, and careful examination of the abdomen, can lead to the correct management in the great majority of cases.

Next article on Emergencies in General Practice.—"Dangerous Bronchitis," by Dr. E. Keith Westlake.

Refresher Course Book.—Copies of the second volume of collected articles from the Refresher Course for General Practitioners are still available at 25s. (postage 1s.) each. The first volume is now sold out.

Clinical Pathology Book.—"Clinical Pathology in General Practice," a collection of 39 articles on clinical pathology that appeared in the *Journal* as part of the Refresher Course for General Practitioners, is now available, price 21s. (postage 9d.).

Both these volumes are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or through any bookseller.

BIOLOGICAL ASPECTS OF DISEASE TRANSMISSION

A symposium organized by the Institute of Biology was held in London on September 29 and 30 and October 1 on "Biological Aspects of the Transmission of Disease." This took a wide view, including veterinary diseases and also those which attack plants, and considering such theoretical matters as the evolution of animal viruses and of trypanosome parasitism, as well as the various factors which control the population of infecting organisms and hence the frequency of disease and the outbreak of epidemics. Over 20 papers were prepared and circulated beforehand as the basis of discussion.

Fungal Diseases

At the first session Dr. G. C. AINSWORTH discussed the spread of fungal diseases. Moniliasis and actinomycosis were world-wide in distribution, the causative organisms being often found in the normal microflora of the mouth without causing any illness, and rarely found apart from man and animals. Spread was probably by direct contact or droplet infection. Ringworm fungi were probably also world-wide, though the diseases they caused were geographically distinct and localized. The reason seemed to lie in unknown environmental factors, possibly in differences in racial susceptibility. *Microsporon audouini*, which causes epidemics of head ringworm in Western Europe, does not seem to establish itself well when introduced into tropical countries, while *Trichophyton ferrugineum*, which is characteristic of the Tropics, fails in Europe. In contrast, histoplasmosis and coccidioidomycosis were fungal infections of the respiratory tract which were chiefly observed in North America in geographically distinct areas.

The development of skin testing had shown that many extremely mild or symptom-free infections must occur. Histoplasmosis is endemic in the central Mississippi and Ohio valleys, and there was a good correlation between the incidence of positive skin test and the occurrence of a certain type of soil. The reservoir of infection was in the soil, and the fungus reached the lungs by dispersal in dust. *Coccidioides immitis* was probably similarly spread, though some workers thought that desert rodents, which are very frequently infected, might be the true natural reservoir of infection, which would then be a matter of contact rather than air spread. Evidently, however, human susceptibility to fungal diseases was much more important than their mode of spread in deciding the appearance of frank cases.

Dr. S. D. GARRETT took up the theme of the soil as a reservoir of pathogenic micro-organisms, but discussed only plant root pathogens, and pointed out that some of these fungi could exist freely in the soil as well as parasitically, while others could manage in dead host tissue but not otherwise. The parasite's range of capabilities decided how well it competed with other species. Dr. J. W. G. LUND (fungal diseases of plankton algae) and Dr. J. E. CROSSE (the dispersal of plant bacterial pathogens) also read papers at this session.

Pathogenic Amoebae

At the second session Dr. R. A. NEAL described the lives of pathogenic amoebae. *Entamoeba histolytica* lives in the lumen of the human gut and in a proportion of cases invades the gut wall and causes the symptoms of amoebic dysentery. Periodically, for unknown reasons, the amoebae of the lumen encyst, and on some days as many as 45 million cysts may be passed in the faeces, while on other days there are none. Spread of the cysts may be by water contamination—as in countries with primitive sanitation—or by flies and cockroaches, which may pass viable cysts for one or two days in their faeces after they have swallowed infective material. Many monkeys are naturally infected, and may be a primitive reservoir of infection. Rats also suffer, but it is thought

that they get this disease by contact with man. *E. coli*, a non-pathogenic parasite the cysts of which are more robust than those of *E. histolytica*, has a very similar life story. Water contamination is the most certain spread, and a single cyst is enough to cause a heavy infection. A recent British survey showed *E. histolytica* in 1.6% and *E. coli* in 24.7% of the population studied.

Bacterial Disease

Professor R. Lovell made the point that the spread of bacterial disease in domesticated animals depends very much on the particular farming methods appropriate to place and climate. Thus anthrax, which is primarily a disease of animals, occurs chiefly in the warm months in swampy areas of countries where it is endemic. The infected animal contaminates its surroundings, and the bacteria multiply and form spores in the decaying vegetation of swamps. In Britain, however, cases of anthrax appear sporadically in the winter among animals fed on imported foodstuffs which carry anthrax spores. A caseous lymphadenitis of sheep is due to *Corynebacterium ovis*, the spores of which contaminate farmyards and enter the animal through skin accidentally scratched during sheep shearing. Tetanus, botulism, and other clostridial diseases occur in animals much as they do in man. The other contributors at this session were Dr. E. L. Taylor on "The Transmission of Helminths of Veterinary Importance" and Dr. C. Horton-Smith on "Factors Affecting the Transmission of Coccidia and the Development of Disease in Fowls."

Types of Transmission

Professor R. Cruickshank sketched out the types of spread of bacterial infection—scarlet fever as the type of dust-borne disease, whooping-cough by intimate contact (direct droplet infection), and measles by floating droplet nuclei, for respiratory infections; food contamination, usually via the hands, from faeces or urine (typhoid) or nose (staphylococcal food-poisoning) in intestinal infections; and all possible routes in skin infections. Professor C. F. Barwell discussed the spread of virus infection from animals to man. Rabbit myxomatosis and canine distemper viruses were apparently so highly adapted to their animal hosts that they would not infect man. But the possibility of virus evolution remained, and sometimes viruses believed harmless to man might suddenly prove otherwise, particularly in laboratory circumstances: Newcastle disease of chickens had been recorded in research workers; and the organism of sheep abortion, economically important in south-east Scotland, caused a severe attack of virus pneumonia. There could be no doubt that some animal viruses would attack man if they were given greater opportunity or a new method of entry to the body. Some were already helped by transport by biting insects, or other trauma (e.g., rabies by animal bites, "cat scratch fever" by thorns, etc.). The pox viruses were an interesting group, because smallpox and chicken-pox enter by the respiratory tract, whereas cowpox and the distinct virus of vaccinia enter through skin abrasions. On the other hand, mouse-pox, common in laboratory colonies, never affected those who handled the animals. One of the best-known animal virus infections of man was psittacosis, spread by pigeons, finches, chickens, and various sea birds, as well as by members of the parrot family. The bird might appear perfectly well and still be excreting virus in the faeces, though a sick bird, such as a sneezing parrot, naturally offered a great risk of infection. Inhalation of dried powdered droppings seemed to be the most important way man caught the illness. Q fever, a natural rickettsial infection of cows and sheep, was another dust-borne illness of man, carried in faeces and on the skin, and also occasionally found in cow's milk, where it resisted the usual pasteurization procedures. Serological testing of blood donors in south-east England, where relatively many cattle are infected, suggested that unrecognized, perhaps symptom-free, cases occurred in people of that district.

Flies and Ticks

Professor G. W. A. Dick, dealing with the spread of viruses by insects, distinguished the purely mechanical from the biological. Thus rabbit myxoma virus could be as well spread by a pin as by *Aëdes aegypti* (a mosquito) or by the European rabbit flea. Poliomyelitis and Coxsackie viruses did not multiply inside biting flies, and there was some doubt whether even mechanical (accidental) transmission was possible: certainly flies were of no epidemiological importance. But yellow fever, for example, multiplied inside *Aëdes aegypti*, and the mosquito, once infected, remained so for the rest of its life, which was not shortened thereby.

Ticks are the vectors of many virus infections: *Ixodes ricinus*, for instance, was the guilty party in louping ill and various epidemics of encephalitis in eastern Europe in the last 10 years or so, though only three cases in man have been described from Britain. This tick is the permanent reservoir of infection, since virus is present in the eggs as well as the adults, and so for generation after generation. In the same section of the discussion P. K. C. Austwick spoke on "Insects and the Spread of Disease," and Dr. Mary Noble on "Transmission of Plant Pathogens by Seed." The following morning opened with a further contribution by F. C. Bawden, F.R.S., on the role of insects, this time in spreading plant viruses, though the principles applied equally to diseases of medical interest and led on to consideration of the control of epidemics with insecticides.

Trypanosomes

Dr. C. A. Hoare, F.R.S., discussed the evolution of parasitism in the protozoan flagellate trypanosomes, starting with the primitive *Herpetomonas* which lives in the mid-gut of the fruit fly *Drosophila* and is passed out in the faeces to infect other flies. Chagas's disease is spread from man to man by blood-sucking bugs: the organism multiplies in the bug, which may drop faeces on the human conjunctiva or other mucous membrane, thus infecting a fresh person. Sleeping sickness trypanosomes multiply in the gut of the tsetse fly, but instead of completing their development there migrate forward into the salivary glands. However, the efficiency of parasitism is here much less, for, while roughly 100% of bugs fed on a mammal infected with Chagas's disease become infective, something in the neighbourhood of only 1% of tsetse flies acquire infection when sucking trypanosome-containing blood. This points to its more recent evolution. Finally, he mentioned an oddity of specialization, the only trypanosome spread from mammal to mammal by direct contact. This was the causative organism of dourine in horses of Southern Europe and North Africa, which is a venereal disease, since it is carried from stallion to mare during copulation.

Malaria

Professor P. C. C. Garnham selected one or two interesting points from the vast field of work on the transmission of malaria. He pointed out how surprisingly rare is true congenital malaria when one considers the flimsy placental barrier between maternal and foetal bloods, and differentiated it from malaria acquired (through abrasions) at birth and only becoming clinically evident after a week or so. He also remarked on the frequency with which malaria was transmitted by blood transfusion in countries such as India, where the disease was anyway endemic. He discussed the reasons why different mosquito species differ so much in their ability to transmit a given species of malarial parasite. The presence of enough para-aminobenzoic acid (P.A.B.) in the mosquito was one biochemical essential, pyridoxine was perhaps another. Any specificity at all was surprising, since the parasite was so adaptable: from a vertebrate biochemical environment at about 40° C. to an intracellular invertebrate one at less than 20° C.

Other tropical diseases were discussed by Dr. O. D. Standen (transmission of schistosomiasis), Dr. D. S.

BERTRAM (transmission of experimental filariasis), and Dr. W. E. KERSHAW (population dynamics of the filariae of man).

Animal Virus Evolution

In the final session Dr. C. H. ANDREWES, F.R.S., discussed the evolution of some animal viruses, what might be termed their archaeology, since their origin, whether from gene or microbe, was not in question, but rather how they had come to adapt themselves to man and other modern animals. He saw the majority of virus infections as being originally spread by insects, and the evolution of air and droplet spread a new feature after man had migrated from the Tropics, where he began, into the temperate zones of the earth. He went further, and imagined that all virus diseases might have begun purely as insect diseases. There are some which affect only insects to-day. Plant viruses are often spread by insects, may multiply inside them, and may do them little harm, and Bawden has suggested that such viruses might have commenced existence in the insects, and secondarily come to attack plants. He offered the behaviour of the virus of lymphocytic choriomeningitis as a possible pattern of evolution. It can be spread among guinea-pigs by mosquitoes and bed-bugs. In a mouse colony the virus was at first spread through excretion in the urine; then it began to be transmitted *in utero* to the young mice, who showed fewer symptoms. Finally the whole colony contained the virus, and all were symptom-free. This was evolution moving at speed before our very eyes.

The symposium ended with papers by Professor W. I. BEVERIDGE on "Properties of Some Infective Agents in Relation to Their Modes of Transmission," and by W. C. MOORE on "The Dissemination of Plant Diseases and Pests in International Plant Trade."

MEDICAL INDEXING AND ABSTRACTING

PROBLEMS OF PUBLICATION

Lieutenant-Colonel F. B. ROGERS, director of the Armed Forces Medical Library, Washington, discussed medical indexing and abstracting services when he addressed the Medical Section of the Library Association in London on September 20. The three main problems of publishing medical indexes were whether the index was to be designed primarily for current search or for retrospective search; whether it was to cover a given subject comprehensively or selectively, and, if the latter, with what degree of selectivity; and the financial resources. The *Index-Catalogue of the Army Medical Library* was an example of a bibliographical tool for retrospective use, while the *Current List of Medical Literature* was for those who wanted up-to-date information. The retrospective bibliography was a legacy from the past and a method still prominent in the humanities to-day. But the situation was different in the sciences and in medicine, where the explosive acceleration of scientific advance made each new work supersede its predecessor to some extent.

Cumulative procedures widely employed in medical indexes were generally good, but the longer the period of cumulation the more severe the strain on the original arrangement of the materials in the index. For instance, a subject might be suitable for a current index, with perhaps twelve articles listed, but it was often insufficiently specific for a five-year accumulation, bringing dozens of pages of references under the same heading.

Comprehensive or Selective?

On the problem of comprehensive versus selective coverage, Colonel Rogers said that the typical medical library, with perhaps 150 current journals, mostly served clinicians (including general practitioners) and was preoccupied with answering simple but important questions. In the highly developed nations of the West, works in the national language could supply whatever was needed by such readers. The kind of index needed in this average situation was one which indexed the 150 periodicals found in the average library. But this would not suit the research worker, who wanted everything in his own field, something in contiguous fields, and an occasional glimpse of what the general practitioner was looking for. Here again the publisher of an index reached a compromise, leaning towards comprehensive rather than selective coverage, believing that this would serve both the research worker and the general practitioner. But here again a price had to be paid. A more comprehensive coverage meant more specific subject headings, which perhaps discouraged the general practitioner and raised production costs. In later discussion Colonel Rogers mentioned that at the Armed Forces Medical Library 50% of the requests to the photo-duplication service were for articles published during the last five years in 135 journals, only 13 of which were in languages other than English.

Financial Difficulties

The publication of a scientific index was not possible without financial subsidies, and this put a limit to its comprehensiveness. Users of medical indexes were unwilling or unable to pay a reasonable price for them. Only 2,000 copies of the *Current List* were being sold throughout the world, although the subscription price paid only for the cost of running off the copies. The *Catalog* of the Armed Forces Medical Library, a unique publication, sold only 250 copies a year. The *Index-Catalogue*, widely praised throughout the world, was on sale for $4.50, but few copies were sold. What was the point of demanding bigger and better medical indexing and abstracting services when those which already existed were not being supported, although they provided tools as good as or better than in any other major field of science?

Colonel Rogers then went on to describe four of the special problems of the *Current List of Medical Literature*: convenience of arrangement, promptness of publication, translation of foreign titles, and methods of abbreviation; and in conclusion he gave some account of the changes taking place or in prospect in his library. Bills before Congress had the object of removing the library from Army control and making it a national medical library. Plans for a new building were in course of preparation, and as soon as they were approved funds for the building itself would be sought. The intention was to maintain the library on its present scale and to continue the bibliographical services which had made it so famous throughout the world.

NEW ACADEMIC YEAR

KING'S COLLEGE HOSPITAL

"Medicine in the Provinces"

At King's College Hospital Medical School the opening of the 126th session on September 30, over which Sir CECIL WAKELEY presided, was marked by an address by Dr. J. H. SHELDON, senior physician, Royal Hospital, Wolverhampton, an old student of King's.

Dr. Sheldon devoted his remarks to the subject of medicine in the provinces, asking what sort of life might one expect to lead as a specialist or consultant in a provincial non-teaching hospital. At least it could now be said that it had become respectable and to be regarded as an objective in itself, and not as a sort of consolation prize for failure to be somewhere else. This had not always been so, but the steady growth in the structure and standards of all the bigger provincial hospitals since the first world war had been quite remarkable. Within his own experience the scene had changed beyond recognition. When he went to Wolverhampton there were four consultants in the town, whereas now there were 34. This steady expansion of the

provincial hospitals, often by as much as tenfold, was a prominent feature of the years between the wars, and had since been accelerated under the National Health Service.

Among the gains of provincial life he would place the sense of civic spirit which came from being a citizen of a town which possessed a corporate sense of individual existence. There were few things more important in the corporate life of a town than the status and reputation of its hospitals, and this in its turn laid on the staff a sense of responsibility to the town as a whole. It was unfortunate that the pressure of modern life made it difficult for the consultant to take that share in the government of his town which was so frequently taken by his predecessors. He laid great stress on the need for the young consultant to identify himself with the town of his choice and to remember that his opportunities there transcended those of merely technical service.

The major professional stimulus of provincial life, Dr. Sheldon continued, came from the wealth of clinical material and the absence of fragmentation in the disposal of clinical problems. It was, in fact, a universal experience, to which all who worked in the larger non-teaching hospitals were fully accustomed, that the young resident fresh from a teaching hospital was surprised at the scale of the material he was called upon to handle. The main hazard of provincial life had been intellectual isolation, accentuated by the absence of students with their salutary influence on the outlook of their seniors, but of recent years the situation had improved out of knowledge with the creation of regional specialist societies. The truth was that after years of uphill struggle the provincial hospitals were beginning to enter into their inheritance, and anyone going there now could be sure of a completely satisfying professional life.

Many years ago he attended a ceremony in the guildhall of an ancient borough in the West Midlands when the freedom of the town was conferred upon a general practitioner. This was a man who had won no prizes at school, nor written any papers afterwards, but for nearly 50 years he had been a busy general practitioner as well as medical officer of health. The speech of the mayor was remarkable for content and brevity: "I hand you this casket, made of Shropshire oak and containing the freedom of the borough, in recognition of a lifetime spent in its service and that of your patients, in which you have served your generation well." No greater thing could be said about a member of their profession.

A vote of thanks to the orator was moved by Mr. HAROLD EDWARDS and seconded by Dr. CLIFFORD HOYLE.

In his report the Dean of the School, Dr. VERNON HALL, said that 48 medical and 18 dental students had begun their clinical training during the year, and altogether there were 291 undergraduates and 17 advanced and research students in the School. During the last 18 months an extension of the School had been planned, the purpose being not to take more students but to provide much-needed accommodation and improved facilities for the present number. It was hoped that building would begin in the spring of 1956.

MIDDLESEX HOSPITAL MEDICAL SCHOOL

A £400,000 Gift

The highlight of the annual dinner of the Middlesex Hospital Medical School on September 30 was the announcement that Colonel the Hon. J. J. ASTOR, chairman of the School Council, had made a gift of £400,000 towards the rebuilding of the school. The Dean, Professor B. W. WINDEYER, said that a rebuilding scheme was planned before the war, but only a small part of it was completed. This year it had again become possible, with the abolition of licences, to proceed with the original intention. The difficulty of obtaining a site had been overcome by the generosity of the Board of the hospital in making some land available, and now came this magnificent donation by Colonel Astor, the latest of many benefactions he had made to the hospital and school. It was hoped that it would be followed by other gifts, because considerably more than this amount, handsome as it was, would be needed.

Sir HAROLD GRAHAM-HODGSON, who presided at the dinner, said that Professor Windeyer, who had now completed his first year as dean, had shown great administrative ability, vision, and kindliness in that office. Those who had had the difficult task of electing a new dean to succeed Sir Harold Boldero could congratulate themselves on having chosen so worthily.

The DEAN said that during and since the war the Central Middlesex Hospital had given valuable assistance in the teaching of some of the clinical students. In a hospital not primarily designed for teaching purposes accommodation problems must have been difficult and have caused inconvenience to the hospital staff. But during last year a building had been erected at the Central Middlesex Hospital to house five resident students and to afford lecture and reading-room accommodation. This year they had been in negotiation with the University of Toronto for a scheme of exchange whereby a physician and a surgeon (using those terms in the widest sense) should go each year to Toronto for one month's hospital service, and at the same time two members of the staff in Toronto should come to the Middlesex. One of the Toronto graduates was present that evening in Dr. IAN MACDONALD.

Dr. J. H. BARON, Senior Broderip Scholar, responded to the toast of the hospital and school, and Dr. W. R. WINTERTON, with some amusing persiflage, proposed the health of the chairman. Among the guests present were LORD MORAN, Sir RUSSELL BRAIN, Sir LIONEL WHITBY, and the Directors General of the Medical Departments of the three fighting services. The company numbered 400.

ROYAL FREE HOSPITAL SCHOOL OF MEDICINE

Physical and Intellectual Adventure

The prize-giving and inaugural address of the Royal Free Hospital School of Medicine took place at the Senate House of London University on September 30 under the chairmanship of Sir FRANCIS LASCELLES. The Dean, Miss KATHARINE LLOYD-WILLIAMS, F.R.C.S., presented her report for the session, after which prizes were distributed by Lady LE GROS CLARK.

In an address of an unusual character, bearing the title "Chant of Pleasant Exploration," Sir WILFRID LE GROS CLARK discoursed on the joys of adventure, physical and intellectual. He described how, many years ago, he was wandering in the forests of Borneo, and, resting on a river bank, with gibbons chattering around him and parrots flying above, he experienced a strange feeling of contentment —a feeling that this was what he had wanted to achieve. He wondered how it was that he found himself in that part of the world at all, and then suddenly he remembered, as a small boy, lying in hospital with scarlet fever and reading a boys' story of exploration in the forests of the Amazon. That reading, with an imagination no doubt already stimulated by his febrile condition, interested him in forest adventure, and he began to understand why he found himself in Borneo. It was the eventual realization of an early emotional urge, or, if they liked, an irrational impulse, and it made him think how much of our behaviour and interest and action in later life was determined by things long forgotten, by early emotional urges. Reason might supply the ostensible motive for the action, but not the underlying motive power. Reason was necessary for guidance and direction, but it was often the irrational impulse which gave the original stimulus.

This experience was particularly interesting to him as a teacher of medical students. He did not know what the procedure of testing and selection might be at the "Royal Free," whether interviewing, examination, or intelligence tests. He hoped it was not the last, because he was very doubtful of their value, and was pretty sure that he himself would have failed to secure sufficient marks to survive them, especially over that type of question which involved mental arithmetic or acrobatics. He sometimes wondered

whether they did not lay too much emphasis on mere intelligence. Of course the student of unusual intellectual attainments or the one who could memorize a mass of facts would always be favoured, but for his own part he would prefer a student of average intelligence with high incentive, perhaps derived from some early emotional urge, to a brilliant student with little or no incentive. The first was bound to succeed, the other might or might not do so. Returning to physical adventure in jungles, Sir Wilfrid Le Gros Clark said that he found Borneo a specially interesting country from the point of view of the comparative anatomist, because every form of animal existence from the highest to the lowest was to be found there. The speaker ended by suggesting that there were plenty of thrills in physical adventure, and still more in intellectual adventure, but he knew of nothing so exhilarating or satisfying to the soul as a combination of both.

Mr. G. Qvist, F.R.C.S., was the proposer and Professor R. E. M. Bowden the seconder of a vote of thanks.

ST. GEORGE'S HOSPITAL

Then and Now

The inaugural address at the opening of the session at St. George's Hospital Medical School on September 30 was delivered by Dr. Anthony Feiling. The Dean, Mr. M. F. Nicholls, presided.

Dr. Feiling, in a reminiscent talk, said that no thinking person could spend more than 50 years of his life as a student and practitioner of medicine without having reached some opinions of his own on medical education and practice. The picture to-day was very different from what it was in those earlier years. The curriculum then was shorter than now, and there was far less specialization. The present-day student would find it difficult to realize the extent to which his predecessors had to rely upon entirely clinical methods of diagnosis. Fifty years ago radiography was practically never used in the medical wards except occasionally for a case of bone disease or for stones in the urinary tract. The radiology of the gastro-intestinal tract, of the lungs, and of the heart simply did not exist. Much greater stress was therefore laid upon careful physical examination, especially in pulmonary diseases.

On the surgical side the greatest difference from present-day experience was the preponderance of septic infections. Every large hospital used to have a special septic ward in which surgical dressers spent a good deal of their time. Modern anaesthetic practice was, of course, quite unknown; gas and ether and chloroform were the only agents used.

Looking at the picture as a whole, Dr. Feiling said that in his early days students were certainly much less supervised than students of to-day. Left much to themselves, they were not spoon-fed with facts nor required to attend so many classes, but had freedom to find their own way to learning—or to ignorance. One major change which had come about in hospital teaching and practice was the advent of specialization, and this had created difficulties in teaching undergraduates. Whatever changes might be contemplated it must never be forgotten that the principle of apprenticeship in clinical medicine—that is to say, the day-by-day instruction of the student at the bedside and in the out-patient room—must be retained. Opportunity must also be given to the student to question and examine patients for himself and to see and hear his seniors doing the same. The student could not learn too soon that he must study the whole man and not merely the pathological lesion. Sympathy and understanding were both requisite. It should not be difficult to supply the sympathy, but a true understanding could come only slowly and from a prolonged study of their fellow men and women. Those who worked in teaching hospitals reminded themselves too seldom how much they owed to their patients, from whose illness and suffering they gained knowledge. He took "this opportunity to acknowledge the debt I owe to those many patients through whom I have been able to pass on something at least of what their sufferings have taught me."

Correspondence

Christmas Gifts Fund Appeal

Sir,—Every autumn an appeal is made to members of the medical profession for contributions to the Christmas Gifts Fund organized by the Royal Medical Benevolent Fund. The appeal has been made for many years, and the very good response is definite proof that the cause meets with approval.

I ask your readers once again to be generous and to send contributions marked "Christmas Gifts" to the Secretary, Royal Medical Benevolent Fund, 1, Balliol House, Manor Fields, Putney, London, S.W.15, so that the less fortunate of our colleagues, or their widows or children, may receive a Christmas present. This brings much happiness and pleasure, and often is the means of making a very real difference to many on Christmas Day.—I am, etc.,

London, S.W.15. Webb-Johnson,
President,
Royal Medical Benevolent Fund.

Prolonged Pregnancy

Sir,—The recent article by Mr. George B. Gibson (*Journal*, September 17, p. 715) on prolonged pregnancy has added another excellent study to our knowledge of post-maturity. The advice given, however, in articles of this sort is invariably coloured by the attitude of the writer towards surgical induction of labour, according to whether he considers it to be a minor obstetric incident or a major surgical hazard. It is as well to summarize our knowledge regarding post-maturity so that the matter may be approached without emotion.

The facts may be stated as follows: (1) The supply of oxygen to any baby will be diminished relatively or absolutely during the weeks following maturity, as shown by Walker.[1] (2) In the absence of intervention a number of babies will suffer death or damage to the central nervous system as a result of this oxygen lack. This damage will generally but not invariably take place in labour. (3) While selective induction should theoretically save numerous babies, it is at present impossible to select cases accurately, as there is no scientific test yet available for foetal anoxia. It is possible to diagnose post-maturity by *x* rays and possible to diagnose maturity of the uterus by an examination of the cervix, but neither of these states is necessarily associated with what might be called post-maturity of the oxygen-supplying mechanism. The date of the last period may on occasion be grossly misleading, for there is no certainty that development of the fertilized ovum may not have been arrested for a significant length of time.[2] (4) It is perhaps not generally realized that a surgical induction of labour with the Drew Smythe catheter will give valuable information as to dangerous post-maturity; for in those cases in which the baby will be at risk in labour there is usually either replacement of the liquor by gelatinous material or else frank meconium staining of the scanty fluid.

It is easy to find an occasional patient in whom surgical induction has apparently led to some complication, and it is much less easy to estimate the benefits conferred upon innumerable women by induction of labour for post-maturity. It is my belief that the dangers of surgical induction are due to imperfect technique and faulty selection of cases. I shall continue to advise that, in every case of presumed post-maturity after consideration of all the factors concerned in the individual case, a manipulation to stretch the cervix and strip the membranes should be performed as an out-patient and a definite date selected for the admission of the patient to hospital for surgical induction if labour has not ensued by that time.—I am, etc.,

Birmingham. W. G. Mills.

References

1 Walker, J., *J. Obstet. Gynaec. Brit. Emp.*, 1954, **61**, 162.
2 Burrows, H., ibid., 1954, **61**, 762.

Foetal Distress

Sir,—I have read with great interest the letters in response to our article on foetal distress (*Journal*, August 6, p. 358), which have produced many valuable observations and suggestions. The letter from Mr. P. Malpas (*Journal*, September 10, p. 675) is characteristically stimulating and contrary. When he states that "whether the rate [of the foetal heart] is a reliable early measure of the foetal tolerance is debatable," he has stressed the essential object of the investigation described.

I would suggest, from the figures obtained, there is a quite definite relationship between the behaviour of the foetal heart and the condition of the child at delivery. However, this relationship is distressingly variable, and is not, therefore, "reliable" in the sense of being acurately predictable on the basis of the simple clinical observations described. In arriving at a wise decision for the individual case, the "percentage risk" associated with the foetal heart signs has been worked out so that it can be given its correct weighting, and added to all the other factors concerned, in arriving at a balanced judgment.

I would agree with Mr. Malpas now, that there is the occasional case in which foetal death in labour occurs without warning.—I am, etc.,

Ashton-under-Lyne. T. B. FitzGerald.

Sir,—Your leading article (*Journal*, September 17, p. 726) prompts me to add a little information derived from midwifery in general practice. Mr. John Stallworthy (*Journal*, August 20, p. 488) suggests to Mr. T. B. FitzGerald and Dr. C. N. McFarlane (*Journal*, August 6, p. 358) that they should consider the cases of the mothers with essential hypertension who give birth to small babies, with small placentas. I do not know whether these cases of mine would be considered as part of that group, because he does not define his criteria for diagnosis of "essential hypertension." The group have, however, always suggested a distinct series to me, and latterly I was able to forecast the infantile risk and prevent it.

The women studied appeared during 420 deliveries in general practice over seven years, and eight births were involved. The following clinical points were observed: (1) In 4 out of the 6 women, over eleven years had elapsed since the last normal birth. In the other 2 only four years elapsed; both births were observed and all 4 babies were at risk. (2) The mothers were over 35 years of age. (3) The resting non-pregnant blood pressure was 160/90 or over. (4) The blood pressure did not rise in pregnancy and there was no albuminuria. (5) The babies, except in two later cases where caesarean births before term were planned, were post-mature (as reckoned by expected dates of delivery). (6) The babies' weights were between 4½ and 5¼ lb. (2 and 2.6 kg.). (7) Two foetuses died before labour, two during labour; one baby died on the second day after birth during cold weather; two were very difficult to resuscitate after birth, although post-mature, and required as much care with heat regulation as a premature baby; one baby had an emergency caesarean birth owing to slowing of the foetal heart, but the baby was born dead; and one baby had an early planned caesarean birth and survived with the normal care required for a premature baby. I am sorry that I did not make any note of the sizes of the placentas.

I should mention that these cases would not be picked up in an antenatal clinic unless notes on their non-pregnant blood pressures were supplied by their family doctors.

I would be glad to give further details of these cases to any doctor wishing to study the problem of foetal distress; also, in all humility, to mention the treatment which I have used.—I am, etc.,

Cockermouth. F. Charlotte Naish.

Sir,—Following the excellent article by Mr. T. B. FitzGerald and Dr. C. N. McFarlane (*Journal*, August 6, p. 358), I would like to add further comment on the management of cases where placental insufficiency is anticipated.

First, to the four factors predisposing to foetal distress one might add a further five—namely, hypertension, cardiac disease, pulmonary disease, prolonged labour (incoordinate uterine action), and pyrexia occurring during labour.

Albeit the authors mentioned that the disappearance of the foetal heart without any warning is very rare, this in fact certainly does occur. Following such a case in a case of post-maturity, where five minutes or less would have been the difference between a live child and a stillborn infant, it was decided that all patients fitting into the above-mentioned nine groups would be put on to prophylactic oxygen early in labour. It will be noted that these conditions are the very ones where gas-and-air to the mother is definitely contraindicated.[1] The oxygen is administered by a plastic mask made by the British Oxygen Company and is of no disturbance whatsoever to the mother. Furthermore, each mother is told the reason for the use of the oxygen, and the response of patients has been admirable—most cases refusing gas-and-air which has been offered later in an attempt to see if the mask is causing any inconvenience. During the period of five months that this study has been going on there have been 825 deliveries. The number of patients receiving prophylactic oxygen—which in a large number of cases later becomes therapeutic oxygen—has been 125—i.e., 15%. A report of this study is being published.

As the authors say in their article, assessment of the effects of treatment is difficult without a control series, and since commencing this therapy it has become so religiously believed to be beneficial that it is deemed unfair to the foetus to deprive it of this often life-saving inhalation.—I am, etc.,

Liverpool, 14. H. Kramer.

References

[1] Russell, Henry S., *British Medical Journal*, 1955, **1**, 909.

Chemotherapy of Bacterial Infections

Sir,—I was interested to read the article by Professor L. P. Garrod (*Journal*, September 24, p. 756), but disappointed to find that in Table V he includes "Labour with manual interference" as one of the conditions in which there is a legitimate use of prophylaxis with antibiotics. Manual interference is presumably the reason for this prophylactic treatment, as such treatment is considered unnecessary in normal labour.

It appears to me that antibiotic prophylaxis is contraindicated for the following reasons: (1) Under modern conditions most patients do not become infected after such "manual interference" and they are therefore exposed to the risks of antibiotic therapy unnecessarily. (2) If they are infected during the operative interference the organisms may well be insensitive to the antibiotic which is employed—in Table III I note that Professor Garrod includes puerperal fever among the conditions in which the effect of an antibiotic is unpredictable. (3) If an infection flourishes in spite of prophylactic treatment the bacteriological identification may be rendered more difficult as the result of this treatment. (4) Prophylactic treatment may cause an infection to remain latent while a patient is in hospital. A flare-up at home will then cause difficulty to the family doctor and criticism of the hospital.—I am, etc.,

Lurgan, Co. Armagh. G. B. Gibson.

Piperazine Hydrate in Ascariasis

Sir,—The report by Dr. L. G. Goodwin and Mr. O. D. Standen on trials with piperazine hydrate ("antepar") in the treatment of ascariasis (*Journal*, December 4, 1954, p. 1332) was received with considerable interest, as the local population in surrounding areas here is heavily infested with this parasite. Treatment previously had been carried out with santonin, but this has not proved to be particularly satisfactory. It was therefore decided to change to piperazine hydrate and to estimate the results in the early cases, using the one-dose method recommended by Goodwin and Standen. In patients over 3 stone (19 kg.) 6 drachms (22 ml.) was given, whilst in children under 3 stone 4 drachms (14.5 ml.) was used. The elixir was administered about

4 o'clock in the afternoon, without any previous preparation of the patient, and a saline purgative was supplied, to be taken the following morning. Patients were told to count, as far as possible, the number of worms passed, and the stools were subsequently examined at a period which varied between two days and two weeks after the administration of the elixir.

Of the 60 patients who received 6 drachms (22 ml.), 23 were still exhibiting ova in the stool when examined afterwards. The number of worms passed varied between one and 36, 7 passing 10 or more. Eleven said that they had not noticed any worms in the stools, although the follow-up examination was negative. Of the 6 young children who received 4 drachms (14.5 ml.), all passed between 3 and 30 worms, although the stool was subsequently still positive for ova in two cases. The dosage mentioned was administered without difficulty and no toxic symptoms were recorded.

The above figures would appear to indicate a failure rate in the region of 40%, although it may be higher than this, as only one specimen of stool was examined after treatment in each case. When heavy infestation is present, however, particularly in children, piperazine hydrate can undoubtedly produce dramatic results, and its ease of administration recommends it in such cases.—I am, etc.,

Accra, Gold Coast. J. J. MESSENT.

Ocular Nerve Palsy with Severe Headache in Diabetics

SIR,—The article by Dr. W. P. U. Jackson (*Journal*, August 13, p. 408) on ocular nerve palsy with severe headache in patients with diabetes mellitus is an interesting report of a subject unfamiliar to the medical profession in general. These lesions may be bilateral.[1] A 62-year-old white man with diabetes mellitus had pain in the eye and paralysis of the third cranial nerve with a sparing of the pupil on the left side. A complete recovery followed. At a subsequent time he had aching in the eye and paralysis of the third cranial nerve on the right side. There was total regression of the symptom and signs. The retention of pupillary function in the otherwise complete paralysis of the left and the right third cranial nerves was unusual. Although the nature and the exact location of the lesion are unknown in these patients, it is the consensus of opinion that it is essentially haemorrhagic and that it is located in the nucleus of the affected nerve. The rapid onset and the slow but usually complete clearing of these lesions are evidence in favour of a haemorrhage rather than the effect of a toxin. The third and the sixth cranial nerves are affected equally. The condition seems to be related to the duration of the diabetes mellitus rather than to its severity, and in this regard it would seem to parallel the experience with the retinopathy of diabetes mellitus. On the large majority of patients the paralysis undergoes spontaneous remission, and there are few, if any, permanent sequelae.—I am, etc.,

Fort Howard, Maryland, U.S.A. JOSEPH M. MILLER.

REFERENCE

1 Earsckson, jun., V. O., and Miller, J. M., *Arch. Ophthal. (Chicago)*, 1952, 47, 607.

Diabetes and Pregnancy

SIR,—Whenever the opinion is expressed that therapeutic abortion is unnecessary, the catchcry of "religious prejudice" is raised by those who defend its use. Dr. W. G. Oakley and Mr. J. H. Peel (*Journal*, September 3, p. 618) have adopted this technique in replying to my letter (*Journal*, August 13, p. 435), in which I stated that their indications for terminating pregnancy in diabetic patients were not tenable *on medical grounds*. Their second line of defence was to suggest that my knowledge and experience of this problem were limited. It is true that my personal experience is limited to 76 cases, and that is precisely the reason why I referred them to the opinion of Dr. Priscilla White.[1] As her opinion was in conflict with theirs, they attempted to circumvent it by stating that (*a*) her writings refer to case series "excluding therapeutic abortion," and (*b*) "she has, like most authors, wisely avoided any attempt to lay down hard and fast indications." It is difficult to see the application of their first point, as her statement obviously implies that she would recommend termination in a certain type of case. With regard to their second point, I would say that she has in fact been quite dogmatic. At the 1954 meeting of the American Diabetes Association there was a panel discussion on "Diabetes and Pregnancy." Dr. Garfield G. Duncan, who acted as moderator, put the following question: "I should like to ask Dr. White to comment on contraindications to pregnancy." Dr. White replied: "I have but one contraindication to pregnancy in a diabetic woman, and that is nitrogen retention or other evidence of renal failure." This is a hard and fast indication, and far removed from the vague generalities enunciated by Peel at Toronto. I agree that pregnancy is not desirable in the type of case mentioned by White. If, however, it has occurred, I do not think that it should be interrupted, as it will not influence the inevitable outcome significantly, and termination of pregnancy carries its own risk. Oakley and Peel then reminded me that a doctor's function in society is "to endeavour to alleviate the pain and suffering of human beings—not to add to them." It is well to remember that a doctor also has a duty to the unborn child.

Reference was made to cases with a bad obstetrical history, in which a row of stillborn babies results in spite of careful and complete control of the diabetes, and it was implied that such cases should be aborted. It appears that they prefer the certain failure of therapeutic abortion to the possibly successful outcome of an uninterrupted pregnancy.

Finally, I would like to ask them what exactly they mean by such observations as "the inherent limitations of the diabetic woman for reproduction" and "the varied dangers and complications affecting both mother and child revealed by a more long-term follow-up." Were their indications for therapeutic abortion to be applied, the diabetic anxious to have children would be much more limited by her physicians than by her disease. It is well, therefore, that an authority like Dr. Priscilla White can now say that there is only one contraindication to pregnancy in a diabetic. The diabetic specialist is following in the footsteps of the phthisiologist and cardiologist, who have found that the best method of dealing with these medical complications of pregnancy is to ignore the pregnancy and to apply the usual medical treatment.—I am, etc.,

Dublin. M. I. DRURY.

REFERENCE

1 White, P., *Diabetes*, 1954, 3, 453.

Snake-bite in Malaya

SIR,—Dr. E. R. S. Hooper (*Journal*, August 13, p. 435) is correct in his belief that no authenticated cases of death in man from the bites of Malayan vipers have been reported previous to Dr. Abdul Wahab Ariff's letter (*Journal*, July 16, p. 204), or, rather, no description of such cases has so far been published. To the authorities quoted by Dr. Hooper might be added T. Cantor,[1] who gathered a very representative collection of snakes whilst in Penang. He also believed that Malayan vipers, though venomous, were not dangerous to human life.

According to statistics in the yearly report of the Medical Department, Federation of Malaya, there were 41 deaths due to snake-bite notified as admitted to Government hospitals in the Federation of Malaya during the six-year period 1946–51. After 1951, cases of snake-bite are included in the category "Accidents caused by bites and stings of venomous animals and insects." Under this heading there were 10, 12, and 17 deaths notified in 1952, 1953, and 1954 respectively. Presumably the majority of these cases were snake-bite poisoning. Of these 80 fatalities, 51 occurred in north-west Malaya. What proportion were due to the bites of *Elapidae*, *Hydrophiidae*, and *Viperidae* respectively is not known, but from my researches on sea snakes I do not think it is likely that many of these notified deaths were due to this cause. Fatalities from sea-snake-bite are not uncommon and may well exceed those due to land-snake-

bite, but, generally speaking, these cases rarely come to hospital or feature in medical statistics. The question of incidence of sea-snake-bites is briefly discussed in a paper recently submitted for publication. As vipers are much commoner than the elapids in Malaya and most cases of envenomation admitted to hospital show the features of viper poisoning, it seems reasonable to assume that the majority of these notified deaths were, in fact, due to viper bites. If this is correct, it is still uncertain whether the mortality was due to direct effects of the envenomation or to secondary complications of infection, etc. With antibiotics, the latter should not nowadays cause death unless the patient comes to hospital a considerable time after the bite. During the course of my researches in northern Malaya I have been told by a colleague of at least two unequivocal cases of death due to haemotoxic snake poisoning personally observed in hospital. In one instance the snake which bit the patient was brought to the hospital. Unfortunately, it was not identified.

It occurred to me that these fatalities in north-west Malaya were probably due to bites of Russell's viper, which has been recorded in Siam but not, so far, in Malaya. Mr. M. W. F. Tweedie, of the Raffles Museum, Singapore, had also come separately to the same conclusion. The matter is of more than theoretical interest, as, if Russell's viper bite occurs in northern Malaya, a tourniquet is indicated, whereas in bites from the species of viper at present recorded in Malaya it is contraindicated because it increases the local necrosis. Furthermore, larger amounts of antivenene would be required than are at present usually given. Investigation of these problems is being carried out.—I am, etc.,

Penang. H. A. Reid.

References

[1] Cantor, T., *Miscellaneous Papers Relating to Indo-China*, 1886, vol. 2, p. 237. London.

Malaria and the Sickling Trait

Sir,—I have read with much interest the two articles on sickle-cell trait with its possible relation to immunity against *P. falciparum* infection (*Journal*, May 14, pp. 1186 and 1189). One confirms the findings originally reported by Allison,[1] whereas the other was not convinced of the significance of Allison's findings.

May I suggest that the proper line of investigation now should be a study of the chemistry of the abnormal S-haemoglobin, its constituents being incorporated in the culture medium for *P. falciparum* in varying concentrations to observe any inhibition of growth of the parasites? It is possible that certain chemical constituents of the abnormal haemoglobin may antagonize some of the parasites' essential metabolites.—I am, etc.,

Calcutta. Shyamal Kumar Sen.

References

[1] Allison, A. C., *British Medical Journal*, 1954, 1, 290.

Modern Treatment of Leprosy

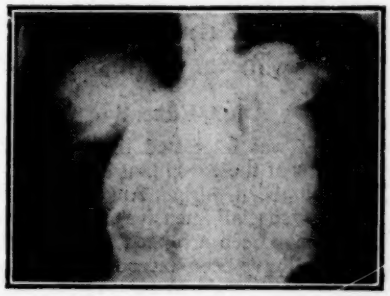
Sir,—Dr. H. W. Wade (*Journal*, August 20, p. 491) has written commenting on my talk before the Royal Society of Tropical Medicine and Hygiene last March (*Journal*, March 5, p. 597), as also did the late Dr. John Lowe (*Journal*, March 26, p. 787). I find myself in the curious position of agreeing broadly and in nearly every detail with my famous critics. This is not really so surprising, because the original talk was of the nature of a mental and spiritual exercise, in which the speaker knowingly stepped out of a comfortable accepted position and attacked that position in order to see what good would come of it. So, from being in the same camp with Lowe and Wade, I temporarily began to attack the position that all is satisfactory in the modern treatment of leprosy.

That some good has come of it is shown by the thoughtful replies of both Dr. Lowe and Dr. Wade, which do a lot to clarify the situation, and in particular the remark of Dr. Wade that my thesis is, after all, only that there is urgent need for improvement in therapy. Hence I think that an attitude of urgent seeking for a speedier and more efficient therapy than that of the sulphones is what should be the residuum of this discussion acceptable to all. This is a real residuum in my own case. In spite of long experience of leprosy amongst Africans, in whom the disease is perhaps more easily treatable and curable than anywhere else, I still long and hope for a therapy which would take under a year to achieve bacteriological negativity. This is for public health reasons of control as well as from the patient's point of view. I share the gratitude for all that the sulphones have done and think that it is no crime nor insult to them to wish for something even better.—I am, etc.,

Busia, Uganda. James Ross Innes.

Diagnostic Pneumoperitoneum

Sir,—I was very interested in Drs. S. C. Truelove and K. Lumsden's article on diagnostic pneumoperitoneum (*Journal*, September 3, p. 585), as I had, myself, employed this procedure in May this year in order to try and establish a firm diagnosis in a woman suspected to be suffering from cirrhosis of the liver. I was not at the time, however, aware of the advantages of the prone position in outlining the subdiaphragmatic organs with air when *x*-raying them. I entirely agree with them on the simplicity and usefulness of the procedure.



The patient, aged 47, was originally admitted to hospital under the care of the dermatologists on account of widespread bullous lesions of the skin. While in hospital she developed oedema of the legs, ascites, a granulocytopenia, and a low platelet count. A provisional diagnosis of cirrhosis of the liver was made. The liver function tests were all within normal limits. Paracentesis abdominis produced 86 oz. (2.5 l.) of straw-coloured fluid. Even after this, examination of the abdomen was difficult, and, although it was suspected on one or two occasions that both liver and spleen could be felt, there was no certainty of this. Since I had worked in a chest unit, I was familiar with the technique of inducing pneumoperitoneum, and I did this with a view to outlining the spleen and liver with air to see if any enlargement could be demonstrated by *x*-ray. This was done and a striking "hob-nail" appearance could be seen on the upper surface of the liver (see Fig.). The spleen was not well outlined, but could be seen to be definitely enlarged. A barium enema showed some evidence of ulcerative colitis. The patient ultimately died, and a necropsy confirmed both the ulcerative colitis and the severe "hob-nail" cirrhosis of the liver.

My thanks are due to Dr. W. S. Thomson for permission to publish details of this case.—I am, etc.,

Leicester. A. W. Reid.

The Whitfield Tradition of Therapy

Sir,—Dr. G. B. Matthews (*Journal*, September 17, p. 737) asks for the original formula of Whitfield's ointment. That given by Dr. David I. Williams in his lecture (*Journal*, August 20, p. 453) corresponds with the one in the 1921 edition of Whitfield's handbook on skin diseases and the ung. ac. benzoic. et ac. salicyl. mite of the King's College Hospital pharmacopoeia of 1914. The latter also contains a "forte" ointment:

Benzoic acid	60 gr. (4 g.)
Salicylic acid	30 gr. (2 g.)
Hydrous wool fat	60 gr. (4 g.)
Soft paraffin	to 1 oz. (31 g.)

The formula of Drs. Wigley and Fox in "Favourite Prescriptions"[1] is therefore a compromise between the two.

The strong ointment was used by Dr. Whitfield for the treatment of multiple warts of the scalp, and very effective it can be. Not that warts all require such firm physical methods, as Dr. Williams explains in his delightful dissertation on them, where he speaks of Whitfield's mercury biniodide and ac. salicyl. in spirit lotion acting like a charm—perhaps as a charm. For Whitfield was a sound psychologist as well as a very great dermatologist, as I know from personal experience. When as a raw houseman I was fortunate enough to be his house-physician I asked him what I should do about a crop of warts on my head. Whitfield said: "Let me see, aren't you sitting for your final M.B. next month? They will all go when you have got through." Sure enough they did.—I am, etc.,

Exeter. R. FORTESCUE-FOULKES.

REFERENCE

1 Wigley, J. E. M., and Fox, F. B., *Practitioner*, 1950, **165**, 33.

SIR,—In reply to Dr. G. B. Matthews's query in your issue of September 17 (p. 737), I have a reprint of an article by Arthur Whitfield himself in the *Lancet* of about 1923, in which he recommends for the treatment of tinea pedis an ointment containing 5% benzoic acid and 3% salicylic acid; so this supports the formula quoted by Dr. David I. Williams in his lecture printed in the *Journal* of August 20 (p. 453) and his letter on October 1 (p. 850).—I am, etc.,

London, S.W.11. M. J. F. COURTENAY.

Adult Education for Consultants

SIR,—I was interested in your article on the continuing education of the consultant by Dr. D. Hubble in your educational number (*Journal*, August 27, p. 505). I would further add that special intensive courses for consultant dermatologists have been arranged by this Institute for the past two years and have been exceedingly successful.—I am, etc.,

J. E. M. WIGLEY,
London, W.C.2. Dean, Institute of Dermatology.

Vaginal Ulceration due to Potassium Permanganate

SIR,—I would like to support the plea made by Dr. E. A. J. Alment (*Journal*, August 27, p. 563) that something should be done to prevent the use of potassium permanganate tablets by women who wish to procure an abortion. I have recently treated a patient in whom the ulceration had involved the right uterine artery. Eight bottles of blood were given to this patient, who, incidentally, was not pregnant.

Since attention was first drawn to this condition by my colleague Mr. J. C. Miller,[1] when he reported 20 cases seen over a period of two years, there has been a steady increase in the number of cases seen at this hospital. I have recently seen five cases in four days, and at the time of writing there are three patients with potassium permanganate burns of the vagina occupying beds in this hospital. Some of these patients pay exorbitant prices for the tablets, while others buy them for a few pence from the chemists.

No amount of publicity is likely to reduce the public's belief in the efficiency of these tablets, which arises from the fact that a great number of the women who use them, although not pregnant, believe that the ensuing haemorrhage is an induced abortion which is followed after an interval by normal menstruation.

If the pharmaceutical chemists would agree not to sell potassium permanganate in tablet form but only as crystals or in solution, the number of cases requiring treatment in hospital would be greatly reduced, as the multiple small superficial ulcers caused by crystals have not, in my experience, caused sufficient haemorrhage to require transfusion or suture. It is to be hoped that some action will be taken by the Pharmaceutical Society in this matter before drastic steps are necessary to restrict the sale of these tablets.—I am, etc.,

Thornton Heath. T. G. E. WHITE.

REFERENCE

1 Miller, J. C., *British Medical Journal*, 1951, **1**, 526.

Duodenal Ulcer Treated by Vagotomy and Gastro-enterostomy

SIR,—In answer to Mr. M. J. Bennett-Jones's suggestion (*Journal*, September 24, p. 793) that the type of gastro-enterostomy might account for the poor results reported by us in a follow-up of patients with duodenal ulcer treated by vagotomy and gastro-enterostomy (*Journal*, September 3, p. 588), I would like to state that we performed a retrocolic posterior gastro-enterostomy with the stoma as close as possible to the pylorus and lying in the long axis of the stomach, which at that level is transverse in the patient.—I am, etc.,

London, W.2. C. G. ROB.

Treatment of Varicose Ulcers

SIR,—The number of treatments propounded for varicose ulcers are legion and most of them far from satisfactory. More than 40 years ago I had the honour to be chosen by Mr. Rutherford Morison as one of his dressers. His treatment was by the proper use of a Martin's bandage. I can see him now holding the bandage up in one hand and telling us he had received more credit by the proper use of it in various capacities than from anything else.

He used it frequently in Bier's treatment. He thoroughly washed the affected part in ordinary soft soap and water and carefully dried it. He then raised the limb and with gentle massage emptied the engorged veins, and then applied the bandage from the instep to just under the knee—the bandage not to be too loose, nor again too tight. He then instructed the patient that he must never remove the bandage till he was in bed, and in the morning to put it on before getting out of bed. The bandage had to be washed in soap and water and to be hung on the end of the bed for use in the morning. The affected leg also had to be washed in soap and water. He also advised five to ten minutes' "cycling" exercise each night in bed. He used the same treatment for varicose veins.

It is surprising what good results can be obtained with this treatment provided the technique is correct. The patient soon learns to apply the bandage at the right tension, which gives a feeling of support to the leg and great comfort to the patient.

Mr. Morison was for many years in general practice at West Hartlepool, Durham. He then decided to give his whole time to surgery and took the English Fellowship and became professor of surgery at the Durham College of Medicine and one of the most noted surgeons of the day. He, years before most others, advocated removal of the appendix at the first possible moment. In the first world war he introduced B.I.P.—I am, etc.,

Gainford, Co. Durham. WILLIAM J. HICKEY.

Milk–Alkali Syndrome

SIR,—Your annotation on the milk–alkali syndrome (*Journal*, September 10, p. 665) prompts me to comment on the following case.

The patient, a man of 39, was diagnosed as having a duodenal ulcer while in the Army, and this was confirmed at operation in 1946. He continued to have periodic but short exacerbations of dyspepsia, with long remissions, until one year prior to admission to hospital in January, 1955, when pain became more severe and exacerbations more frequent. Despite liberal use of alkalis and diet, his pain persisted and he was admitted for a period of strict medical treatment.

On routine examination a blood pressure of 190/130 mm.Hg was recorded; the urine contained a trace of protein but no other abnormalities, and the blood urea was 81 mg.%. On bed-rest the blood pressure fell to 130/100 mm. Hg after seven days, but the blood urea rose to 110 mg.%. A urea clearance test revealed 30% of normal renal function and on intravenous pyelography there was no evidence of renal excretion up to one hour after injection. A bilateral retrograde pyelogram showed a normal appearance

on both sides. The blood pressure after two weeks had fallen to 130/80 mm. Hg, while the blood urea remained raised at 110 mg.%.

At this stage the possibility of alkalosis due to excessive alkali ingestion was considered, and, on questioning, the patient admitted that he had for several months been taking up to ¼ lb. (113 g.) of proprietary alkaline powder (mainly sodium bicarbonate) each day, apart from his one to two pints (1.1 l.) of milk daily. All alkaline mixtures were withdrawn, and a personal supply of alkaline powder was removed from his bedside locker. Within one week his blood urea had fallen to 53 mg.% and in a further week to 38 mg.%. At this stage an intravenous pyelogram showed that both kidneys excreted the dye. He was discharged on aluminium hydroxide and has remained free of pain for several months.

I wish to thank Dr. R. R. Hughes, under whom this patient was admitted for treatment.—I am, etc.,

Bebington, Cheshire. A. G. SHAPER.

Low Backache

SIR,—I read Dr. R. N. Wilson and Mr. S. Wilson's article (*Journal*, September 10, p. 649) with great interest and pleasure, and am glad to see that someone, at last, is trying to find a method of treating low backache in a logical way—i.e., to replace that which is displaced in order to reduce the loss of earnings and the time off work.

The excellent co-operation described in this paper between doctor and physiotherapist must be extended in and outside hospitals, and is certainly the way to rapid alleviation of backache. This is shown by the authors' figures, which are similar to my own published in a letter to the *B.M.J.* (February 12, p. 412) stating that, of those cases of lumbar disk protrusions treated by manipulation, 57% were pain-free after one treatment and over 75% after two treatments. All lumbar movements and straight-leg raising were tested in all cases before and after manipulation. I am sure all medical men who deal with low backache, especially general practitioners and those preventing industrial invalidism, would like to know the quickest method of giving relief. Can anyone produce figures of an alternative treatment to manipulation which show better results? Is there any way of dealing with a recent displacement more likely to be effective than immediate anatomical restoration?—I am, etc.,

London, W.1. R. BARBOR.

Methylpentynol

SIR,—Recent correspondence on the subject of methylpentynol prompts me to report the following two cases. These cases demonstrate the risks inherent in the hitherto easy availability of a drug which relieves certain psychiatric symptoms and which may be considered as a possible suicidal agent.* In this respect the very lack of side-effects such as occur with other substances used for the relief of symptoms, such as reserpine and chlorpromazine, may be a disadvantage. The first of these cases shows certain features which could be due either to the withdrawal of therapeutic effect or to the true withdrawal symptoms of a drug of addiction.

A flight-sergeant aged 31 had been drinking heavily since 1946, but while overseas from 1952 to 1954 he was consuming up to two bottles of brandy a day. On return to this country he found the cost of this prohibitive, and by chance he read an article in the popular press on methylpentynol, learned it was "a sort of alcohol," and tried it and found it effective in giving him the same sort of "kick" as he got out of drinking. It has previously been reported that in the normal subject no such kick is produced by its use. From May, 1954, he has been taking 8 to 10 capsules on waking to face the day without tremor. In addition, over this period he was supplementing the capsules with such alcohol as he could afford. This had continued to the present time (May, 1955), and over the past month he has been reported as being perpetually "drunk"—slurred speech, ataxic gait, and coarse tremor. On one occasion he found himself without capsules one morning and developed an uncontrollable trembling, sweating, and feeling generally ill. The symptoms were immediately alleviated by taking methylpentynol one hour later. It is difficult to decide whether this was a true withdrawal reaction or an anxiety state. It is interesting to note that he was capable of work while taking this high dosage combined with alcohol for a period of nearly one year.

The second case was that of a sergeant nursing orderly aged 34 suffering from a severe reactive depression, who attempted suicide with methylpentynol. He bought a tin of 100 capsules one week before his attempt for use as a sedative. He took about 46 capsules of 250 mg. for this purpose. He then took approximately 26 capsules in two doses (12 at night and a further 14 in the morning, about seven hours later). He was found at 3 p.m. to be just rousable, with slurred speech. He remained drowsy for a further 24 hours but had no other ill effects.

A fatality has been recorded in a previously healthy woman who took 18–24 capsules.[1] One patient has been known to take 50 capsules and suffer no ill effects apart from diarrhoea. In another instance[2] recovery from the ingestion of 10 g. methylpentynol has been reported, and it certainly seems that as a potential suicidal agent the chances of a fatality resulting are negligible compared with barbiturates or coal gas.—I am, etc.,

Aylesbury. JOHN J. BRADLEY.

REFERENCES

1 Cares, R. M., Newman, B., and Mauceri, J. C., *Amer. J. clin. Path.*, 1953, 23, 129.
2 Brown, I. M., and Ellis, R. A., *British Medical Journal*, 1955, 1, 268.

*As from August 15 methylpentynol became a Part 1 Schedule 1 poison, and, although still obtainable without prescription, its sale will now require a signature in the Poisons Book.

Cerumenolytic Agents

SIR,—"Cerumol" can be shown by a simple *in vitro* test to be far more efficacious in disintegrating ear wax than untreated oils such as olive oil. There would appear to be no reason why this action in the test-tube should not also take place in the outer ear. The experiment with several cerumenolytic agents (sodium bicarbonate and glycerin solution, olive oil, hydrogen peroxide, and cerumol), reported in the *Journal* of September 17 (p. 722), however, comes to a different conclusion.

Without going into detailed criticism of the plan of the experiment itself, we believe the most likely explanation of this apparent failure of cerumol is due, in fact, to the procedure followed in the application of the agents. The report states: "Each such subject . . . was sent into the syringeing room, where five drops of one of the solutions under trial were placed in the meatus and sealed in with a plug of cotton-wool." In the type of case selected for this test the liquid would at first pool upon the hard wax and would be liable to absorption by the cotton-wool plug. Cerumol spreads very quickly into cotton-wool—more quickly than olive oil. We believe that the greater part of the cerumol was taken up by the cotton-wool and was not left free to act on the wax. In our opinion, therefore, the test was vitiated by this failure of technique, certainly so far as cerumol was concerned.—I am, etc.,

London, N.16. J. RABINOVITCH,
Director,
Laboratory for Applied Biology Ltd.

Fibrocystic Disease of the Pancreas

SIR,—As an overseas member I open the *Journal* with particular pleasure, and recently was delighted with Dr. James H. Hutchinson's very interesting article (*Journal*, August 6, p. 339) and your leading article (p. 367) on fibrocystic disease of the pancreas.

I wonder, however, how many of your readers agree that surgical relief of the obstruction in meconium ileus is not often successful, at least in avoiding neonatal death. The results after 1949 of the surgical service at the Boston Children's Medical Centre, which were quoted by Dr. Harry Shwachman in a monograph,[1] have been a survival of 15 out of 19 patients. This suggests a less gloomy immediate prognosis, although the ultimate one is unchanged.—I am, etc.,

Boston, Mass., U.S.A. A. C. EVANS.

REFERENCE

1 Shwachman, H., *Advanc. Pediat.*, 1955, 7, 249.

Barbiturate Poisoning

Sir,—We believe this to be the first recorded instance of the successful use of "megimide" (bemegride) and "daptazole" (amiphenazole) in treating severe barbiturate poisoning in a child 15 months of age.

The patient, a girl weighing 1 st. 10 lb. 3 oz. (11 kg.), had accidentally taken about seven 3-gr. (0.2 g.) capsules of "tuinal" (quinalbarbitone sodium and amylobarbitone sodium) at 2 p.m. on September 2, 1955. When brought to the Woolwich Memorial Hospital at 4.45 p.m. she was moribund, cyanosed, cold and clammy, had hardly any respiratory excursions, a very rapid and thready pulse, hardly countable, pinpoint pupils, reacting very sluggishly to light, completely flaccid limbs, and absent reflexes. Two ml. of nikethamide were given intramuscularly without noticeable improvement. An endotracheal tube was passed and oxygen given continuously under positive pressure. Her stomach was aspirated and about 15 ml. of gelatinous fluid withdrawn. The stomach was then washed out with about 300 ml. of water. At about 6.15 p.m. (one and a half hours after admission) very shallow spontaneous respirations at 40 per minute were observed. Normal saline was then administered through a polythene cannula into the internal saphenous vein at the left ankle, at a rate of 10 drips per minute.

At 6.19 p.m. a series of five injections each of daptazole (0.5 ml.) and megimide (5 ml.) was commenced, there being an interval of three minutes between the first and second injections, five minutes each between the second and third and the third and fourth injections, and 12 minutes between the fourth and fifth injections. Following this fourth injection (25 minutes after the first injections) the pupils were dilated (2 mm. diameter) and reacted actively to light. The respirations were now 29 per minute and deeper. The pulse was of good volume, rate 128 per minute. The knee jerk on the right was brisk (the left leg was in a splint). The biceps and triceps jerks were elicited after a further 17 minutes (7.01 p.m.). The tone in the limbs was also returning, and the child withdrew her limbs actively when they were pinched. Oxygen inhalation was stopped at 6.30 p.m., since the respirations were spontaneous and quite deep. The endotracheal tube, however, was left in.

As the patient maintained her improvement after the fourth injection, she was transferred to the ward at 7.45 p.m., where she was given penicillin, 50,000 units intramuscularly. About 45 minutes after admission to the ward her reflexes were becoming sluggish and her limbs flaccid. She showed no sign of voluntary movements, coughing, or swallowing. Hence, at 8.36 p.m. (1 hour and 45 minutes after the last injection of the first course), the injections were recommenced, 0.5 ml. of daptazole being followed immediately by 5 ml. of megimide. The second injection was at 8.52 p.m. and the third at 9.01 p.m. The next three were given after 7-minute intervals and the final two injections of this second course after 5-minute intervals. Seven minutes after the eighth injection at 9.33 p.m. (the last one of the second course) she moved her limbs voluntarily and swallowed for the first time. Her pulse was 135 per minute and of good volume, and respirations were 29 per minute. Her pupils reacted actively to light and were 2 mm. in diameter and the tone in her limbs began to increase. The reflexes, however, were not quite as brisk as they were when they first appeared at 6.44 p.m. (knee jerk) and 7.01 p.m. (biceps and triceps jerks).

As it seemed that the "safe state" had been reached, the injections were suspended. For the next hour or so her pulse rate ranged between 135–140 per minute. The pulse was of good volume, respirations were 29–30 per minute. The reflexes, pupil reactions, and tone of limbs were much the same as when they returned at 9.40 p.m., but the child did not swallow or continue to move her limbs about spontaneously and she did not react to stimulation as actively as she had done before. Hence, at 10.36 p.m., the third course of injections was commenced—0.5 ml. of daptazole immediately followed by 5 ml. of megimide—at five-minute intervals. About five minutes after the fourth injection (at 10.53 p.m.) she actively moved her limbs, swallowed and yawned, and, for the first time, coughed. Soon spontaneous movements of her head occurred. The endotracheal tube was removed (at 11.15 p.m.) and a sucker used to clear the air passage of mucus, etc.

During the next hour she moved her limbs and head spontaneously, and she actively resisted when her air passage was being sucked out. She also coughed frequently and twice cried out feebly. At 2.40 a.m. a plantar response (extensor) was elicited for the first time. At 3.20 a.m. the child began to cry and continued crying for three minutes. She groaned and actively resisted aspiration of the air passage. For the first time her plantar response was flexor. From then on the slightest provocation evoked the most violent resentment.

In all, the patient had 4,250 mg. of megimide, 127.5 mg. of daptazole, and two-thirds of a pint of saline intravenously. Thiopentone sodium was always available in case of toxic signs developing. She continued to have 50,000 units of crystalline penicillin intramuscularly three times a day. During the morning of September 3 she was very irritable, whimpering and crying at the slightest disturbance. At 3 p.m. she recognized her parents and talked for the first time.

Two observations stand out clearly from this case: first, megimide and daptazole may be used with perfect safety by the intermittent method of administration in a very young child. Secondly, these drugs should be given until all the signs of the "safe state" have appeared, especially spontaneous movements, coughing, swallowing, and phonation.

We wish to thank Dr. David Morris, consultant paediatrician to the Woolwich group of hospitals, for permission to publish this case; Dr. J. V. Armstrong, physician superintendent, Brook General Hospital, for his invaluable advice and help in treating this child; and Dr. A. Edmund Allcock, medical officer, Nicholas Products Laboratories Ltd., for his encouragement and advice.—We are, etc.,

M. S. Perinpanayagam.
Grace Nicholls.
J. D. Osmond.

London, S.E.18.

Aortic Stenosis

Sir,—We are distressed at the violent exception taken by Sir Russell Brock (*Journal*, October 1, p. 851) to the reference to him in our article on aortic stenosis (*Journal*, September 24, p. 759). It is, of course, a vital distinction that he allows pressure measurements obtained at thoracotomy from each side of the aortic valve to influence his decision whether or not to proceed to aortic valvotomy *only* when the thoracotomy is performed for some primary purpose other than aortic valvotomy itself. We apologize most sincerely for the misrepresentation of his views which has resulted from our failure to make this distinction.

It should not be necessary to point out that our aim was to note the importance which Sir Russell Brock attaches to such measurements, not to question his ability to decide when thoracotomy is indicated. We mentioned the matter only because we doubt the validity of measurements of pressure, particularly without simultaneous measurements of blood flow, in a circulation which is so dependent on the activities of the anaesthetist. It has been our experience that when the patient is anaesthetized, and the chest open, the systemic pressure may, in extreme cases, be almost half, and the heart rate almost double, the values obtained preoperatively. It is clear that Sir Russell Brock is himself aware of these fallacies.—We are, etc.,

M. B. Matthews.
W. E. Medd.

London, S.E.1.

POINTS FROM LETTERS

Courses in Tuberculosis

Professor F. Heaf (Cardiff) writes: You refer in your Education Number (August 27, p. 554) to the courses in tuberculosis arranged by the Tuberculosis Education Institute and by the University of Wales. To avoid misunderstanding, I should like to explain that the department of tuberculosis of the Welsh National School of Medicine runs two courses during the year: the first is on tuberculosis and diseases of the chest and lasts from the beginning of October to the end of November; and the second is for the Tuberculous Diseases Diploma and is from the first week in January until the end of June. These two courses are organized by the Medical School and are quite distinct from the short three- or four-day refresher courses which are arranged at Sully Hospital (Sully, Glam.) by the Tuberculosis Educational Institute.

Psychology and Psychiatry in Medical Education

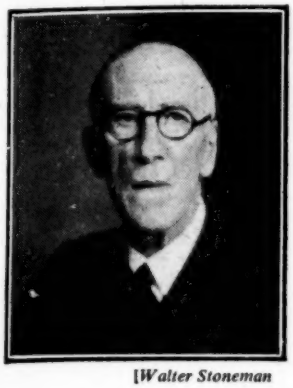
Dr. Amy Pantin (Cambridge) writes: Dr. Desmond Curran (*Journal*, August 27, p. 515) has not checked his literary references as carefully as he has his scientific ones. The lines he attributes to Andrew Marvell were written some two hundred years nearer our time by George Meredith. They occur in the long poem "Modern Love."

Obituary

H. M. TURNBULL, D.M., F.R.C.P., F.R.S.

We record with regret the death on September 29 of Professor H. M. Turnbull, emeritus professor of morbid anatomy in the University of London. He was 80 years of age, and he died in the London Hospital, where for forty years he was director of the Pathological Institute.

Hubert Maitland Turnbull was born in Glasgow on March 3, 1875, and was educated at Charterhouse and Magdalen College, Oxford, where from the study of classics—he took a second-class in Classical Moderations in 1896—he turned to physiology, winning the Welsh Memorial Prize in 1899, a prize awarded for the best set of drawings illustrative of human anatomy by a student. At the London Hospital, where he won the Price scholarship and the Anderson prize in 1900, he graduated B.M., B.Ch. in 1902, taking the London Conjoint diploma in the same year. He held a Radcliffe travelling fellowship from 1904 to 1906, spending the two years at the universities of Copenhagen and Dresden. He proceeded to the D.M. in 1906, was elected a Member of the Royal College of Physicians in London in 1924, and became a Fellow of the College in 1929.



[*Walter Stoneman*

From Dresden, where he acted as Professor Schmorl's voluntary assistant, Turnbull returned to the London Hospital and was appointed director of the Pathological Institute, which became the Bernhard Baron Institute of Pathology in 1927; he held the appointment until 1946, when he retired. Recognized as a teacher of pathology by the University of London in 1912, he was given the title of reader in 1915, and four years later was appointed to the chair of morbid anatomy. During the course of his career Turnbull published a number of papers on morbid anatomy in *Brain*, in the *Quarterly Journal of Medicine*, and in other journals, and he was the author of some of the Special Reports published by the Medical Research Council. He was also editor of and a contributor to the "Archives of the Pathological Institute of the London Hospital." Two issues of the *Journal of Pathology and Bacteriology* were published in his honour—the first in 1945 when he reached the age of 70, and the second in 1946 when he retired. In 1939 he was elected a Fellow of the Royal Society, and six years later the University of Oxford conferred on him the honorary degree of D.Sc. He was an examiner in pathology at Oxford from 1913 to 1916.

Fishing was one of Turnbull's recreations, and in 1909–10 he contributed a series of articles to *The Field* on the scales of salmon. As a young man he played Association football for Oxford against Cambridge and for the United Universities eleven against London. He married Miss Catherine N. Arnold in 1916, and had three sons and one daughter. Mrs. Turnbull died in 1933.

D. S. R. writes: To those who were trained by him H. M. Turnbull was an inspiring chief. He brought to the study of morbid anatomy a thoroughness of method and unswerving devotion to truth which were consciously designed by him to raise the subject to the level of a science. His election as F.R.S. in 1939 was most welcome as a mark of his achievement. If, then, this objective has been attained to-day, the part he played in the early years of this century merits full recognition. It must be recalled that when Turnbull embarked upon the subject of his choice in 1906, fresh from his experiences in Schmorl's laboratory in Dresden, morbid anatomy was in the doldrums. The rapid progress of research in bacteriology and serology had convinced many that morbid anatomy had had its day, with the result that it often received perfunctory attention, at least in this country. Turnbull insisted, from the start, upon complete and systematic dissection of the body at post-mortem examinations, the storage of all microscopical preparations, and objective reports the items of which were entered in card-indexes. He was set against reliance upon a single staining method for diagnostic purposes, and progressively introduced new specific stains in the interests of precision and research. As a monument to his method the records of the Bernhard Baron Institute of Pathology now form a unique collection, the value of which in research has repeatedly been proved.

His own industry was immense, and his reputation as a special pathologist soon attracted graduates from other centres, both in this country and abroad, who came to work in the Institute as voluntary assistants. While many of Turnbull's pupils have as pathologists carried his methods and ideals to other centres, his influence also penetrated the clinical sphere. Other pupils became consultant physicians and surgeons, and their teaching and research were inspired by the truth and objectivity of Turnbull's methods. The London Hospital has owed more to him perhaps than to any other man by virtue of his long-sustained influence.

Much of Turnbull's own work is embodied in the detailed reports prepared for the publications of clinical colleagues, and also in the publications of his numerous pupils. He was responsible for a number of Special Reports issued by the Medical Research Council, and that on "The Accuracy of the Wassermann Test" (1920) is a remarkable compendium of macroscopical and microscopical observation. His study on arteries, entitled "Alterations in Arterial Structure, and their Relation to Syphilis" (1915), is a classic of such importance that it should compel the attention of any worker in this field. The pathology of bones was his favourite interest, dating from his period of study with Schmorl, whose methods he brought back to this country and subsequently improved. His publications in this field form but a small fraction of his observations, and it is to be regretted that he was so often diverted from his writing either by the demands of others or by the physical sufferings that too frequently interrupted his work. Moreover, his innate passion for truth often deterred him from publishing work in which he suspected some minor flaw. While there are few systems of the body in which existing knowledge is not enriched by one or more contributions from his pen, it should be added that the central nervous system vied with the skeleton in his interest. His name is particularly associated with the identification and description (1926) of post-vaccinal encephalitis, a condition which he first observed in 1912 and more fully in the years 1922–3. But, owing to the embargo laid upon the publication of these cases by the Ministry of Health, his report was delayed until after the Dutch cases appeared in the press (1925).

In his person Turnbull was of distinguished appearance. His tall lean figure and the pride and sensitivity of his ascetic face will not be forgotten by those who met and knew him. As a colleague once commented: "You feel at once that you are in the presence of a great man." This, combined with a certain reserve of manner and an unconcealed distaste for all forms of slipshod thinking, made him at times appear formidable, and his colleagues could be chastened by the exposure of their incomplete mental processes. A closer

acquaintance revealed his intense loyalty to his colleagues, especially those who worked for him, his deep sympathy with and understanding of human problems, and also his intense altruism. Unknown to most, he spent long hours in organizing relief measures on behalf of colleagues, or their families, who were in difficulty. He enjoyed many outdoor pursuits and was a keen geologist, bird-watcher, golfer, and fisherman. Visits to the Chelsea Flower Show revealed him as a specialist in rhododendrons, and the issue of acrid fumes from his room after the summer vacation was sure evidence that he was engaged in making preparations of sundry rocks for polariscopic examination.

Turnbull's retirement was delayed by the last war. Even so, it had been hoped that he might enjoy some years in which he could work on his unfinished problems in bone-pathology. Most regrettably his prolonged ill-health prevented this. While deploring this deprivation, those who knew him, or came under his influence, will remember his long life of high purpose and devoted work with a sense of thankfulness and inspiration.

HAROLD BURROWS, C.B.E., Ph.D., M.B., F.R.C.S.

Mr. Harold Burrows, consulting surgeon to Gosport Hospital, died in St. Bartholomew's Hospital, London, on September 29. He was 80 years of age.

Harold Burrows was born in India on April 8, 1875, the son of Surgeon Major E. P. Burrows, and was educated at Marlborough College and at St. Bartholomew's Hospital, graduating M.B. in 1899. Two years later he took the F.R.C.S. Burrows always retained a deep affection for St. Bartholomew's, where his father had been before him and where two of his sons followed him. During his student days at the hospital he came particularly under the influence of C. B. Lockwood (later a Bart's surgeon) and Sir Lauder Brunton, who perhaps may have had something to do with Burrows's physicianly approach to surgery. For a time he was prosector at the Royal College of Surgeons, and to eke out his income he was assistant editor of *The Hospital* under Sir Burdett Coutts. His first surgical appointment was to the staff of the Bolingbroke Hospital, Wandsworth, and two years later, in 1905, he became senior assistant surgeon to the Seamen's Hospital, Greenwich. In 1907 he moved to Southsea on his appointment to the staff of the Royal Portsmouth Hospital, where he was greatly helped by another Bart's man, Henry Rundle. As a Territorial he was called up in 1914, and went to France in the following year with the 20th General Hospital. Later he became consulting surgeon to the First Army and to the Army of the Rhine. He was twice mentioned in dispatches, and in 1919 was appointed C.B.E. After resuming his busy consulting practice in Portsmouth and Southsea he helped greatly with the development of the Gosport War Memorial Hospital, and with the encouragement of Sir Robert Jones he organized the collection of funds for providing orthopaedic services in Portsmouth and the surrounding area. In 1920 he was awarded the Jacksonian Prize of the Royal College of Surgeons of England, where he was appointed a Hunterian professor in 1922 and again in 1933 and 1935. When the British Medical Association held its Annual Meeting at Portsmouth in 1923 he acted as one of the honorary secretaries of the Section of Surgery, and in the following year at Bradford he served as a vice-president of the Section. Among his more important publications were articles on tetanus and gunshot wounds of blood vessels in Barling and Morrison's *Manual of War Surgery* (1918). He was also the author of *Pitfalls of Surgery* and *Surgical Instruments and Appliances Used in Operations.*

In 1925 a prolonged illness forced him to abandon clinical work, and he turned to cancer research, becoming experimental biologist in the Research Institute (later the Chester Beatty Research Institute) at the Royal Cancer (now Royal Marsden) Hospital. Here he carried out much experimental work, his special interest being in the sex hormones. In 1932 he published a monograph entitled "Some Factors in the Localization of Disease in the Body." A few years later, at the age of 63, he took the degree of Ph.D. at London University. His major work, *The Biological Action of Sex Hormones*, was first published in 1944, and eight years later he was co-author with Dr. E. S. Horning of a book entitled *Oestrogens and Neoplasia*. Only a few months ago he contributed an article on this subject to *St. Bartholomew's Hospital Journal*.

In 1945 he retired to Marlborough, where he happily continued his scientific writings and occupied his little spare time with gardening. He was twice married. By his first wife, formerly Miss Lucy M. E. Wheeler, he had two sons, one of whom, Mr. H. Jackson Burrows, is the well-known orthopaedic surgeon. In 1927 he married Miss Gwendoline M. Paul, by whom he had one son, who died in 1952 while a student at Bart's.

M. D. writes: In these days, in which technology is tending more and more to replace clinical judgment, the remembrance of men like Harold Burrows is an inspiration. He had indeed a true scientific background, of which he never lost sight, as is evident from his research in later life, expressed in some of his publications. But he never allowed this aspect of his work to assume an undue proportion in his surgical practice or to overcloud his primary objective, which was to achieve, in the light of his own practical experience, the utmost that was possible for the ultimate benefit and the greatest comfort of the individual patient. To-day there are too few who seem able to realize the vital difference between a "surgeon" and an "operator." Burrows was essentially an example of the former. His operative technique, though adequate, was not spectacular. The value of his work lay, not in the speed or in any unusual dexterity with which his operations were carried out, but in the care and thoughtfulness with which treatment was planned beforehand and continued so long as the patient remained in hospital or nursing-home. Nothing was too much trouble; no detail, either during operation or in the after-treatment, which could affect the patient's comfort and subsequent well-being was omitted. These are qualities essential to a good surgeon, and such indeed he was.

Burrows was a naturally shy man, and to those who did not know him or who had not worked with him his manner was apt to suggest a certain diffidence. However true this may have been in respect of his personal relations with strangers, it was certainly not so in his professional work, in which coolness of judgment was combined with wealth of experience and an unerring memory for the lessons of the past. By the death of Harold Burrows the profession has lost yet another clinician of the old school, trained in all the best traditions of the science and art of surgery, whose mode of approach to the problems which doctors are called upon to solve should serve as a model for the student of to-day and for future generations.

C. H. WALKER, M.B., F.R.C.S.

Mr. C. H. Walker, who practised as an ophthalmic surgeon in Bristol for many years, died at his home in Bristol on September 29 aged 94.

Cyril Hutchinson Walker was born at Malton, Yorkshire, in 1861, the youngest of the five sons of the Rev. John Walker, rector of Bradwell, Norfolk. From Haileybury College he went on to Jesus College, Cambridge, and he completed his medical training at the London

Hospital, where for a time he was dresser to Sir Frederick Treves. Graduating M.B. in 1887, he held a resident appointment at the London Hospital and then became successively junior and senior house-surgeon at the Royal London Ophthalmic Hospital. Leaving Moorfields in 1890, he was appointed ophthalmic surgeon to the Bristol General Hospital. Three years later he took the F.R.C.S. and shortly afterwards was elected to the staff of the Bristol Eye Dispensary and the Bristol Eye Hospital. He was also a lecturer in ophthalmology to the University of Bristol. During the first world war he served as a major in the R.A.M.C.

Mr. Walker remained in practice in Bristol until 1933, but after his retirement he continued to be an active member of the committees of the Bristol Eye Hospital and Blind Asylum until 1953. Even in old age he remained very energetic and often went out shopping alone. He did not give up driving a car until over the age of 90. For two years in succession (1933 and 1934) he was Master of the Oxford Ophthalmological Congress, and in the two succeeding years president of the Ophthalmology Section of the Royal Society of Medicine. He was also a past-president of the Bristol Medico-chirurgical Society. He joined the Ophthalmological Society of the United Kingdom in 1888, and was vice-president from 1921 to 1924, and an *ex officio* member of the council until 1935. He held office in the Section of Ophthalmology at several Annual Meetings of the B.M.A., being secretary of the Section in 1894 and vice-president in 1904 and again in 1925.

In 1900 Mr. Walker married Dr. Caroline Green, who died suddenly two years ago. He leaves three daughters and two sons, one of whom is a doctor. One of his grandsons is also medically qualified.

S. H. T. writes: Although he was a remarkably deft operator, Cyril Walker will not be remembered predominantly as an academic teacher or a shrewd surgeon, but as a very humble gentleman with a boundless sense of humour, constant thoughtfulness for others, and a practical living Christian faith. He spoke little of his many attainments, even when pressed. He had many interests, but probably foremost was his garden, in which after his retirement he spent most of his time. He used to tell of the "elephant man" (made famous by Sir Frederick Treves) who lived at the back of a small shop near the London Hospital, and of operations when he was a student. Less than a year before he died he described the details of a rapid total glossectomy that he had seen as a student. He used to speak of his grandfather, born in 1782, who always took his gun with him when driving down to Bond Street from Hampstead in his coach, so that he could shoot the wild duck in the marshy pools that are now Regent's Park.

GORDON WHITEHEAD, M.B.

Dr. Gordon Whitehead, consulting venereologist to the United Manchester Hospitals, died at his home at Cheadle Hulme on September 25.

Gordon Whitehead was born on May 17, 1886. He studied medicine at Manchester, graduating M.B., Ch.B. (Vict.) in 1911. At that stage of his career he was thinking of taking up general surgery, and held the appointment of resident surgical officer first at Ancoats Hospital, Manchester, and then at the Royal Infirmary, Bradford. During the first world war he served in the R.A.M.C. and became a surgical specialist in the British Expeditionary Force in France. On demobilization he realized how great the need was for someone with his training to build up a first-class genito-urinary service in Manchester, and his efforts were rewarded in 1931 when he was appointed to take charge of the large genito-urinary section of the venereal disease clinic at the Manchester Royal Infirmary. Shortly afterwards he was appointed lecturer in venereal diseases at the University. When the National Health Service came into being, Dr. Whitehead was appointed consulting venereologist to the United Manchester Hospitals.

P. B. M. writes: With the passing of Gordon Whitehead Manchester has lost its pioneer venereologist. By his medical colleagues and his friends Gordon will long be remembered with affection and respect. His stocky figure, husky voice, and assertive carriage were characteristics peculiar to the man. When temporarily frustrated his temper remained even. When an objective was achieved he never crowed over his opponents. Perhaps one's happiest memories are to be found in the recollection of his fund of stories—some Rabelaisian, but always entertaining and appropriate. His non-professional interests were wide. For many years he acted as medical officer to one of the largest professional football teams in the North of England, only resigning in protest when he found his advice on the fitness of a player was overruled by other considerations. His integrity was unshakable. At Old Trafford his happy presence was welcome to many members. One incident may be selected to illustrate his puckish humour and innate courage. Two years before his death Whitehead was severely stricken with coronary thrombosis, and a compassionate posting was sought for one of his serving sons. Certificates provided by his advisers were more than serious in their import and prognosis. Accidentally these came into the patient's possession, and for many weeks he read them to all and sundry with great glee in that he had proved them fallacious. He leaves behind him a widow and two sons, to whom our sympathy is extended.

Mr. J. D. McCULLOCH, for many years consultant ophthalmic surgeon to Bradford Royal Eye and Ear Hospital and to Bradford Royal Infirmary, died on August 27 at the age of 74. James Duff McCulloch was born at Latheron, Caithness-shire, on September 11, 1880, the son of Principal J. D. McCulloch, D.D., and was educated at Glasgow High School and Glasgow University, where he graduated M.B., Ch.B. in 1903. After holding the appointments of casualty officer and senior house-surgeon at Sheffield Royal Infirmary, he settled in practice at Bradford in 1908, becoming also clinical assistant and assistant surgeon at the Royal Eye and Ear Hospital, appointments he held until 1922, when he became honorary ophthalmic surgeon to the hospital and to Bradford Royal Infirmary. He was also on the staff of other hospitals in the area, among which were the Batley and District Hospital, the Bradford Children's Hospital, and the Skipton and District Hospital, and his knowledge and experience were freely offered to the Bradford Institution for the Blind. A member of the British Medical Association for 48 years, he was chairman of the Bradford Division from 1928 to 1930, and when the Association held its Annual Meeting at Bradford in 1924 he acted as one of the honorary secretaries of the Section of Ophthalmology. He leaves a widow.

Mr. IVOR LLOYD writes: Although Mr. J. D. McCulloch was no longer in practice, having retired in 1946, his many activities kept him among us until his recent illness. He had to undergo a major thoracic operation and appeared to make a good recovery. Soon afterwards he had a relapse which caused his death within a very short time. Entering general practice at Bradford in 1908, he soon established himself and became a well-respected and trusted practitioner. His interest in ophthalmology developed and was advanced by an assistant position at the Bradford Royal Eye and Ear Hospital. In 1922 he decided to devote his full time to the specialty and was appointed as consultant surgeon to the hospital and the Royal Infirmary. Faithful service to those hospitals, and in fact to the whole region,

until his retirement in 1946 will be remembered with affection by his colleagues, assistants, and the general staff. His knowledge of the specialty was very wide, and he was a superb diagnostician and surgeon. Although rather quiet and retiring in manner, he had a forceful personality combined with great organizing ability, and no one ever came to "Jimmy" for assistance or advice and went away empty-handed. Even after his retirement his help was frequently sought for problems requiring the judgment of a mature, keen mind. He led a busy life, for, apart from an extensive surgical practice, he was an active member of the Ophthalmological Society of the United Kingdom and the North of England Ophthalmological Society. Despite this he somehow managed to find time for his garden, which was a constant source of relaxation and pleasure, and, as if life was still not full enough, he became a mason and devoted much time and labour to the craft, attaining Grand Lodge rank; the loss of such a man will be keenly felt in masonic circles. His friends will mourn the passing of a true Scottish gentleman.

Dr. J. L. Cochrane, who died at his home at Kendal, Westmorland, on September 18 at the age of 68, had practised in Kendal since 1912, except for the war years 1914–19, when he served in France with the R.A.M.C., winning the Military Cross in 1917. Born on February 9, 1887, James Lang Cochrane was educated at Glasgow University, where he graduated M.B., Ch.B. in 1909. For very many years, besides conducting a large and successful general practice with his brother, Alexander Ebenezer Cochrane, who died in 1953, he was an honorary surgeon at the Westmorland County Hospital. In addition to his professional duties he found time for a great deal of public work. He had been a county councillor since 1928 and served with distinction on the health and education committees, and more recently had been chairman of the children's committee since its formation. In 1937 he was made a county magistrate, and was also actively connected with a large number of charitable undertakings. A member of the British Medical Association for forty-five years, he was honorary secretary of the former Kendal Division from 1922 to 1926, chairman from 1929 to 1932, and president of the old North Lancashire and South Westmorland Branch in 1928–9. He also served on the local medical committee for many years and on the executive council since 1948.

Dr. R. G. Mathews writes: James Cochrane was a strong personality with decided views and firm convictions, and as such he was always forthright in debate and a fearless advocate of individual rights and responsibilities. But he never lost his keen sense of fun. He will best be remembered by his patients and colleagues on committees as a kindly, lovable man who never spared himself (or anyone else) in his endeavour to uphold the best traditions of medical practice as he knew it, and always insisted on the importance of preserving the personal relationship in the face of changing conditions.

Mr. Frederick Melville, the first full-time secretary of the Society of Radiographers, died in the Middlesex Hospital on September 21 at the age of 64. Mr. Melville had a long and close association with the medical profession. After returning from war service in France in 1918 he was attached to the War Office *x*-ray laboratory until 1923, when he was appointed by Sir Grafton Elliot Smith to take charge of the new *x*-ray department established in the Institute of Anatomy at University College, London. In 1927 he was elected to the council of the Society of Radiographers and in December of that year was appointed honorary secretary and treasurer. Later he became whole-time secretary of the Society, a post he held until 1954, when ill-health necessitated his taking a less arduous task. Mr. Melville was a founder member and vice-president of the Board of Registration of Medical Auxiliaries, and represented the Society of Radiographers on the Board from 1936 until his death.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 17** (No. 37) and corresponding week 1954.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	9	2	4	0	2	9	1	6	0	0
Dysentery	417	69	267	11	3	305	34	161	0	2
Encephalitis, acute	3	0		1		3	0	0	0	
Enteric fever:										
Typhoid	4	1	1	0		5	2	0	0	
Paratyphoid	116	14	2	5		10	1	2(B)	1	
Food-poisoning	490	77		13		224	9		1	
Infective enteritis or diarrhoea under 2 years				32	89				22	27
Measles*	1,038	22	24	10	26	1,286	87	154	20	35
Meningococcal infection	11	0	21	1	1	23	0	11	2	
Ophthalmia neonatorum	22	1	7	0		39	0	3	0	
Pneumonia†	164	8	100	2	1	230	15	109	1	
Poliomyelitis, acute:										
Paralytic	193	29	64	1	5	58	3	9	2	2
Non-paralytic	218	24				34	3			
Puerperal fever§	213	32	14	2		201	37	7	1	
Scarlet fever	329	18	54	18	9	426	20	82	14	29
Tuberculosis:										
Respiratory	590	66	111	15		740	67	111	43	
Non-respiratory	74	7	19	2		100	9	22	5	
Whooping-cough	1,142	46	54	45	74	1,688	67	113	8	20

DEATHS in Great Towns	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	1	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	2	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	6	0	1	0	3	6	1	0	1	1
Influenza	2	0	0	0	0	2	0	0	0	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	1				0	1		
Pneumonia	102	16	6	2	2	122	19	14	4	4
Poliomyelitis, acute	7	1	1		0	1	0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	48	9	8	3	4	69	10	9	3	1
Non-respiratory		1	1	0	1		0	11	1	1
Whooping-cough	4	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	180	16	34	4	11	175	22	17	5	13
Deaths (excluding stillbirths)	4,143	591	471	85	142	4,340	625	497	78	137
LIVE BIRTHS	6,971	1043	847	192	406	7,152	1030	804	211	342
STILLBIRTHS	197	26	17			185	22	25		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Poliomyelitis

In England and Wales in the week ending September 24 notifications of acute poliomyelitis numbered 394, of which 201 were paralytic and 193 non-paralytic. There were 8 more cases of paralytic and 25 fewer cases of non-paralytic poliomyelitis than in the previous week. Deaths in the great towns numbered 7, the same as in the previous week. Notifications from the beginning of the year up to September 24 numbered 4,251; only in 1947 and 1950 have they been more numerous, with 6,193 and 6,033 respectively.

The incidence decreased in the northern, north-western, midland, eastern, and south-western regions, in Wales, and in the East and West Ridings of Yorkshire; it increased in London and the south-eastern region, and in the north midland and southern regions. The following districts have had particularly high rates to date (figures are for cases notified by September 24, with rates per 100,000 of the population in parentheses): Barnsley C.B., 76 (101.5); Willesden M.B., 143 (80.6); Mexborough U.D., 15 (78.9); Hoyland Nether U.D., 12 (75.8); Wombwell U.D., 13 (69.2); Cheshunt U.D., 15 (59.2); Dover M.B., 19 (55.8); Stepney M.B., 52 (53.1); Poplar M.B., 37 (51.6).

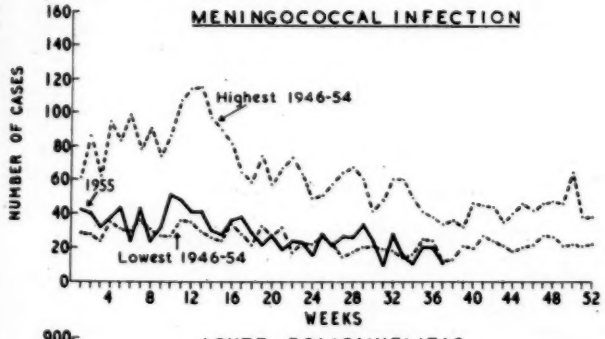
In Scotland 44 cases were notified, 20 fewer than in the previous week; 27 of them were reported from Glasgow. There were 4 deaths.

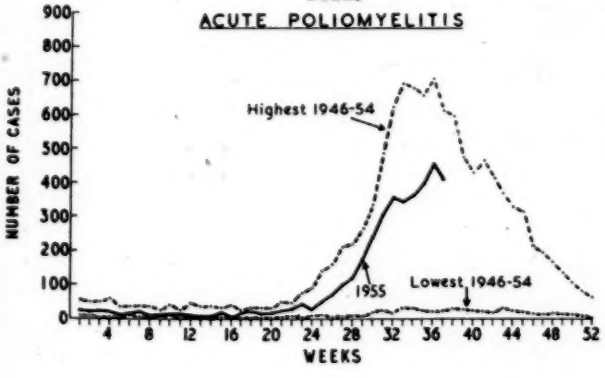
Week Ending September 24

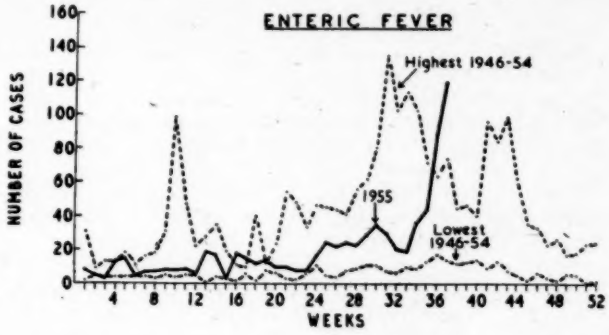
The notifications of infectious diseases in England and Wales during the week included: scarlet fever 426, whooping-cough 1,113, diphtheria 6, measles 1,082, acute pneumonia 171, acute poliomyelitis 394, dysentery 450, paratyphoid fever 69, and typhoid fever 6.

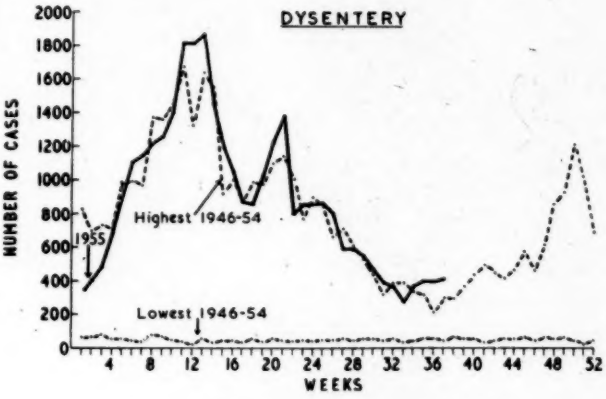
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1946–54 are shown thus ------, the figures for 1955 thus ———. Except for the curves showing notifications in 1955, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

The largest fluctuations in the trends of infectious diseases in England and Wales during the week ending September 17 were decreases in the number of notifications of 625 for measles, from 1,663 to 1,038, 407 for food-poisoning, from 897 to 490, 319 for whooping-cough, from 1,461 to 1,142, and 47 for acute poliomyelitis, from 458 to 411, and increases of 62 for scarlet fever, from 267 to 329, and 30 for paratyphoid fever, from 85 to 115.

The incidence of measles continued to decline throughout the country; the largest falls in the number of notifications were 79 in Sussex, from 118 to 39, and 79 in Glamorganshire, from 165 to 86. The number of notifications of whooping-cough was the lowest for almost three years; the largest falls during the week were 57 in Durham, from 141 to 84, 53 in Yorkshire West Riding, from 177 to 124, 39 in Northumberland, from 59 to 20. The largest rise in the number of notifications of scarlet fever was 16 in Middlesex, from 6 to 22. 9 cases of diphtheria were notified, being 3 more than in the preceding week; 3 cases were notified in Birmingham C.B.

The number of notifications of paratyphoid fever was the largest for any week since 1941. The largest outbreaks were Nottinghamshire 71 (Worksop M.B. 28, Kirkby-in-Ashfield U.D. 25, Basford R.D. 10, Beeston and Stapleford U.D. 5), and London 14 (Hackney 9, Shoreditch 5). The numbers of notifications in these two counties last week were 43 and 18 respectively. The only new outbreak during the week was 9 cases in Dorsetshire (Weymouth and Melcombe Regis M.B. 6).

417 cases of dysentery were notified, being 18 more than in the preceding week. The largest returns were Lancashire 110 (Liverpool C.B. 27, Preston C.B. 15, Blackpool C.B. 11, Stretford M.B. 11, Blackburn C.B. 10, Manchester C.B. 9), London 69 (Chelsea 33, Hackney 9), Yorkshire West Riding 45 (Leeds 14, Bradford C.B. 13), Middlesex 23, Durham 23, and Yorkshire North Riding 18 (Middlesbrough C.B. 17).

In Scotland the notifications of dysentery numbered 267, 1 more than in the preceding week. The chief centres of infection were Glasgow 169, Dundee 20, Edinburgh 18, Stirling county 11, Ayr 10, and Kirkcaldy 10. The number of notifications of acute poliomyelitis declined from 78 to 64. The largest return was 39 from Glasgow.

Record Infant Mortality Rates

In England and Wales the infant mortality rate in the quarter ending June 30 reached a new record low level for the quarter of 24.4 per 1,000 related live births. (The quarter ending September 30 normally has a lower rate than the June quarter.) The rate for England and Wales for the whole year 1954 was 25, also a record low level; for Wales only it was 32. The infant mortality rate for Scotland in 1954 was 31 per 1,000 live births, for Northern Ireland 33, and for the Irish Republic 38. It was 22 in both Australia and New Zealand, and 32 in Canada. The lowest reported rate was in Sweden, with 19. The rate in the U.S.A. was 27.—*Registrar-General's Quarterly Return for England and Wales, No. 426.*

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in August was 114, compared with 105 in the previous month and 86 (revised figure) in August, 1954.

The numbers of cases of industrial diseases in the United Kingdom reported during August, 1955, were as follows: lead poisoning 4, aniline poisoning 3, chronic benzene poisoning 1, anthrax 2, epitheliomatous ulceration 19, chrome ulceration 10; total 39. There was 1 death from chronic benzene poisoning, and 1 from epitheliomatous ulceration due to mineral oil.—*Ministry of Labour Gazette*, September, 1955.

Outbreak at Royal Free

Only sporadic cases are now reported of the obscure infectious disease causing an outbreak at the various branches of the Royal Free Hospital. In the week up to October 3, 1 new case and 2 suspected cases were reported. The Gray's Inn Road Hospital has been reopened.

Medical News

Anaesthetists' Federation.—During the world congress of anaesthetists held in Holland in the first week of September the World Federation of Societies of Anaesthesiologists came into being. Its foundation was the culmination of the work of an interim committee which had been formed in Paris in 1951 under the chairmanship of Dr. Harold Griffith, of Canada. This committee has had the help and advice throughout of Dr. J. F. Delafresnaye, Secretary of the Council for the International Organization of Medical Sciences. The Federation started its independent life with a full meeting of the elected delegates of 26 national societies of anaesthetists forming the general assembly. There were present also observers from societies not yet ready to become full members of the Federation. Among these were the official observers from the United States and Soviet Russia. Dr. Harold Griffith (Canada) was elected the first president and Dr. Ritsema van Eck (Netherlands), Dr. A. Goldblat (Belgium), Dr. Rudolf Frey (Germany), and Dr. Manuel Gurbelo (Cuba) vice-presidents. Dr. Geoffrey Organe (Great Britain) was elected to the office of secretary-treasurer. He will carry on the business of the Federation with an executive committee elected by the general assembly until the next congress. On this committee of 12 there are two representatives of the Association of Anaesthetists of Great Britain and Ireland. The object of the Federation is "to make available the highest standard of anaesthesia to all the peoples of the world." The secretariat will be in London.

Joint Tuberculosis Council.—At its next meeting the Joint Tuberculosis Council will consider increasing the number of constituent organizations. The council is composed of representatives of societies and other organizations concerned with the study, control, and treatment of tuberculosis and other respiratory disorders. Its principal functions are to act as an advisory body and to prepare and publish memoranda on relevant subjects. The annual subscription is three guineas. Any society not already represented on the council may apply for membership to the Hon. Secretary, Dr. R. L. Midgley, Hawkmoor Chest Hospital, Bovey Tracey, Devon, before November 16.

New Antibiotics Factory.—A year ago the late Sir Alexander Fleming visited the new plant for the production of antibiotics then being built by Pfizer Ltd. at Richborough, near Sandwich, and he placed a commemorative foundation cap in position, prior to the installation of the fermenters. Guests at the formal opening of the factory last week saw the huge fermenters in action, one of them resting on a support bearing the inscribed metal plate commemorating Sir Alexander Fleming's visit. At the opening ceremony Lord Brabazon of Tara paid a tribute to the British and American scientists whose work had made the project possible. A sample of soil dug up by Lord Brabazon in the factory grounds was flown the same day to New York, where it will be tested for the presence of antibiotic-producing organisms. The new factory at Sandwich, which cost £2½m. to build, is already producing enough "terramycin" (oxytetracycline) to meet British needs, and the products of the factory—"tetracyn" (tetracycline) as well as terramycin—are being exported to nearly all the countries in the sterling area and to Europe. In describing the research which had preceded the discovery of terramycin, Mr. J. J. Powers, senior vice-president of the parent American company, said that more than 100,000 samples of soil were analysed and £4m. spent on the chemical, biochemical, and engineering development that led to the commercial production of the antibiotic.

Sir Henry Dale, O.M., F.R.S., and Lady Dale were the guests of honour at a dinner held jointly by the Physiological Society and the British Pharmacological Society on September 27, at the Royal College of Surgeons, to celebrate Sir Henry's 80th birthday, which fell earlier this year. Professor E. B. Verney, F.R.S., was in the chair and presented the many messages of greeting from Sir Henry's friends and pupils abroad. Sir Charles Lovatt Evans, F.R.S., proposed the toast to Sir Henry Dale. After Sir Henry's reply, Professor Verney proposed the health of his fellow guest and octogenarian, Professor Winifred Cullis. Professor Z. M. Bacq moved the toast to "The Society," and Professor J. H. Burn, F.R.S., Professor J. H. Gaddum, F.R.S., Dr. W. Feldberg, F.R.S., and Professor G. L. Brown, F.R.S., told reminiscences of their times with Sir Henry. After Professor Heymans had read some greetings from Belgian academies, Professor A. V. Hill, F.R.S., expressed to Mr. Julian Taylor, Vice-President of the Royal College of Surgeons, the thanks of the Societies to the Royal College for their most generous hospitality, and moved that the meeting adjourn for ten years until Sir Henry's 90th birthday.

Social Welfare.—The National Council of Social Service is preparing the tenth edition of its directory of national voluntary organizations. In order to make this publication as complete as possible, the council would be glad to receive information about social welfare organizations set up since 1951 or which may be set up before the spring of 1956. Its address is 26, Bedford Square, London, W.C.1.

COMING EVENTS

Sheffield Old Students.—The Sheffield Medical School Old Students' Association will hold its annual dinner on October 15 at the Royal Victoria Hotel, Sheffield, at 6.30 for 7 p.m. All members are invited to attend.

St. Luke's Day.—Cardinal Griffin will celebrate Mass in the Crypt of Westminster Cathedral on October 23 at 8.30 a.m. for the Westminster Branch of the Guild of St. Luke, SS. Cosmas and Damian. All Catholic doctors are invited.

Ophthalmological Society of the United Kingdom.—Annual congress will be held on April 26–28, 1956, at the Royal Society of Medicine, London. The main subject for discussion will be "The Early Diagnosis of Glaucoma." Members wishing to contribute should notify the hon. congress secretary at 45, Lincoln's Inn Fields, London, W.C.2, not later than November 30. The annual dinner will be on April 26, 1956.

NEW ISSUES

British Journal of Pharmacology and Chemotherapy.—The new issue (Vol. 10, No. 3) is now available. The contents include :

Actions of Succinylcholine Chloride on the Circulation. K. Vidal Beretervide.
Some Chemical and Physical Properties Associated with Histamine Antagonism. P. B. Marshall.
The Development of Tolerance and Cross-tolerance to Methonium Compounds in Laboratory Animals. J. K. Mohanty.
The Action of Local Anaesthetics on Experimental Epilepsy in Cats and Monkeys. C. G. Bernhard and E. Bohm.
Nomograms for Multiple Slope-Ratio Assays Arranged in Blocks, and Improved Nomograms for Assays without Blocks. Pamela M. Clarke.
The Effects of Glycyrrhetinic Acid on Salt and Water Metabolism. E. E. Galal.
Enzymic Oxidation of Derivatives of Ethylenediamine. H. Blaschko, M. L. Chatterjee, and Jean M. Himms.
In vivo and in vitro Comparative Assays of the Anticoagulant Activity of Dextran Sulphate and Heparin. E. Grasset and D. E. Schwartz.
The Metabolism of ^{32}P-labelled Triethylenephosphoramide in Relation to its Anti-tumour Activity. A. W. Craig and H. Jackson.
Superfusion as a Method for the Study of Drug Antagonism. G. W. Cambridge and J. A. Holgate.
The Effect of Chlorpromazine on Adrenocortical Activity in Stress. P. A. Nasmyth.
Chemical Constitution and Anthelminthic Activity of Cyclic Analogues of Phenothiazine. W. P. Rogers, J. Cymerman-Craig, and G. P. Warwick.
Antifungal Activities of Bis*iso*quinolinium and Bisquinolinium Salts. H. O. J. Collier, M. D. Potter, and E. P. Taylor.
The Action of Eserine on the Blood Pressure of the Rat. V. Varagic.
Antagonism of Acetylcholine by (+)- and (−)-Hyoscyamine. P. B. Marshall.
Effect of Nicotinhydroxamic Acid Methiodide on Human Plasma Cholinesterase Inhibited by Organophosphates Containing a Di-alkylphosphato Group. F. Hobbiger.
The Mechanism of After-discharges Caused by Veratrine in Frog's Skeletal Muscles. B. Delisle Burns, George B. Frank, and G. Salmoiraghi.
Injections of Bulbocapnine into the Cerebral Ventricles of Cats. W. Feldberg and S. L. Sherwood.
The Pharmacology of an Iron-dextran Intramuscular Haematinic. L. E. Martin, C. M. Bates, C. R. Beresford, J. D. Donaldson, F. F. McDonald, D. Dunlop, P. Sheard, E. London, and G. D. Twigg.
The Pharmacological Properties of the Optical Isomers of Benzhexol, Procyclidine, Tricyclamol, and Related Compounds. W. M. Duffin and A. F. Green.
The Effect of Cortisone Alone and in Combination with Isoniazid in Experimental Corneal Tuberculosis in Mice. M. Naguib and J. M. Robson.
The Treatment of Experimental Bacillary Infections of Mice with Quinoxaline 1:4 di-N-oxide. C. E. Coulthard and L. J. Hale.

Issued quarterly ; annual subscription £4 4s.; single copy 25s.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, October 10

Chelsea Clinical Society.—At Rembrandt Hotel, Thurloe Place, S.W., 8.30 p.m., discussion to be opened by Dr. E. Lincoln Williams: Alcoholism.
Institute of Neurology.—5 p.m., Sir Charles Symonds: Value of Symptoms in Neurology.
Postgraduate Medical School of London.—4 p.m., Dr. I. C. Gilliland: Exophthalmos.
●Royal College of Surgeons of England.—5.15 p.m., Professor A. G. R. Lowdon: Surgery of the Biliary Tract; 6.30 p.m., Sir Clement Price Thomas: Resection for Pulmonary Tuberculosis.
University College London: Department of Pharmacology.—At Physiology Theatre, 5.30 p.m., Professor J. F. Danielli, Ph.D.: Physico-Chemical Mechanisms of Drug Action.

Tuesday, October 11

Institute of Dermatology.—5.30 p.m., Dr. C. O. Carter: Genetics in Dermatology.
●Institute of Neurology.—5.30 p.m., Professor D. Slome: Physiology of Pain.
Oxford University Medical Society.—At Radcliffe Infirmary, 8.15 p.m., Dr. A. M. Cooke: The Forerunner.
●Royal College of Surgeons of England.—5.15 p.m., Mr. A. Dickson Wright: Painful Arm; 6.30 p.m., Mr. C. Naunton Morgan: Carcinoma of the Rectum.
St. Mary's Hospital Medical School.—At Wright-Fleming Theatre, 5 p.m., Mr. A. W. Bourne: Hypertension in Pregnancy.
West End Hospital for Neurology and Neurosurgery.—5.30 p.m., Dr. J. N. Milnes: neurological demonstration.

Wednesday, October 12

Edinburgh University: Faculty of Medicine.—At Anatomy Lecture Theatre, University New Buildings, Teviot Place, 5 p.m., Macarthur Postgraduate Lecture by Dr. D. A. Mitchison: Factors Limiting the Efficiency of Chemotherapy of Tuberculosis.
Harveian Society of London.—8.15 p.m., Dr. Desmond Curran: Some Problems Raised by Murderers, Including Heath, Haigh, Christie, and Straffen.
Institute of Dermatology.—5.30 p.m., Dr. R. W. Riddell: Role of Fungi in Skin Diseases.
Institute of Diseases of the Chest.—4.30 p.m., Dr. F. H. Young: Pathogenesis of Tuberculosis II.
Oxford University.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Professor Carl V. Moore: Nutritional Aspects of Iron Deficiency.
Postgraduate Medical School of London.—2 p.m., Dr. D. I. McIlwaine: Methods of Biochemical Study of the Brain.
●Royal College of Surgeons of England.—5.15 p.m., Mr. William Gissane: Surgery of the Hand; 6.30 p.m., Sir Geoffrey Keynes: Surgery of the Thymus Gland.
●Royal Faculty of Physicians and Surgeons of Glasgow.—5 p.m., Mr. W. M. Dennison: Advances in Surgery of Infancy and Childhood.
St. Mary's Hospital Medical School.—At Wright-Fleming Theatre, 5 p.m., Dr. M. J. O'Neill: lecture-demonstration in psychiatry.
Society of Chemical Industry: Food Group.—At Linnean Society, Burlington House, W., 6.30 p.m., Professor J. Yudkin, Dr. D. Sheppard, Ph.D., and Dr. M. Abrams, Ph.D.: Factors Affecting the Choice of Food.

Thursday, October 13

Alfred Adler Medical Society.—8 p.m., Dr. A. Denis Leigh: Present Status of Psychosomatic Medicine.
Guthrie Society.—At Meyerstein Lecture Theatre, Westminster Hospital Medical School, 8 p.m., Sir Norman Birkett: Books and Lawyers.
Institute of Neurology.—5 p.m., Dr. W. Noordenbos (Amsterdam): Pain of "Central Origin."
Liverpool Medical Institution.—7.30 p.m., reception and Inaugural Address by the President: A Surgeon and Seven Pieces of Old Silver.
●London University.—At Queen Elizabeth College, 5.30 p.m., Sir Russell Brain, P.R.C.P.: Dr. Johnson and Science.
North-western Tuberculosis Society.—At Clinical Theatre, Manchester Royal Infirmary, 5 p.m., Presidential Address by Dr. A. Clark Penman: After Bodington.
●Nuffield Orthopaedic Centre, Wingfield-Morris Orthopaedic Hospital, Oxford, 8.30 p.m., Mr. F. G. Allan: Leg Equalization, with Special Reference to Bone Lengthening.
●Royal College of Surgeons of England.—5.15 p.m., Sir Russell Brock: Surgery of the Great Vessels; 6.30 p.m., Mr. T. G. I. James: Tumours of the Stomach—other than Cancer.
Royal Eye Hospital.—5.15 p.m., Dr. T. H. Whittington: Aspects of Refraction—I. Attributes of Normal Vision.
St. Andrews University.—At Physiology Department, Queen's College, Dundee, 5 p.m., Sir Wilfrid E. le Gros Clark, F.R.S.: Problems of Muscle Growth and Regeneration.
St. George's Hospital Medical School.—5 p.m., Dr. D. Curran: post-graduate demonstration in psychiatry.
Surrey Inter-hospital Psychiatric Association.—At Banstead Hospital, Sutton, Surrey, 7.30 p.m., Symposium: Management of the Long-stay Schizophrenic Patient. Papers by Dr. A. A. Baker, Dr. G. M. Carstairs, and Dr. A. Ritchie.
University College London: Department of Biochemistry.—At Physiology Theatre, 5 p.m., Dr. J. Monod (Paris): Specific Factors in the Biosynthesis of Enzymes.

Friday, October 14

●Institute of Dermatology.—5.30 p.m., clinical demonstration by Dr. R. M. B. MacKenna.
Institute of Diseases of the Chest.—5 p.m., clinical demonstration by Sir Clement Price Thomas.
Institute of Laryngology and Otology.—4.30 p.m., annual address by Mr. F. C. W. Capps: Association Between Dermatology and Oto-rhino-laryngology.
Postgraduate Medical School of London.—(1) 2 p.m., Mr. W. Blackwood: Some Aspects of the Pathology of Transtentorial Herniation. (2) 4 p.m., Dr. A. M. Cooke: Problem of Osteoporosis.
●Royal College of Surgeons of England.—5.15 p.m., Professor Digby Chamberlain: Carcinoma of the Stomach; 6.30 p.m., Mr. E. W. Riches: Place of Total Cystectomy in the Treatment of New Growth of the Bladder.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Brodie Russell.—On September 26, 1955, at the Stanley Nursing Home, Chester, to Pamela (formerly Cooper), wife of Dr. Iain Brodie Russell, a daughter.
Glover.—On September 12, 1955, to Dr. and Mrs. J. Edward Glover, of "Warke House," Mellalien Street, Middleton, near Manchester, a second son.
Thomas.—On September 20, 1955, at University College Hospital, London, W.C., to Joan (formerly Bowker), M.B., B.S., wife of Ian Davies Thomas, M.B., M.R.C.P., M.R.A.C.P., a son—Mark Alfred Bowker.
Tyrrell.—On September 10, 1955, at Sheffield, to Dr. Moyra Tyrrell (formerly Wylie), and Dr. David Tyrrell, a son—Stephen.
Williams.—On September 23, 1955, at 155, Andover Road, Newbury, Berks, to Moza, wife of Dr. P. M. de C. Williams, a third daughter.

DEATHS

Dickson.—On September 13, 1955, at Aird House, Inverness, Alexander Dickson, M.B., F.R.C.S.Ed., Group Captain, R.A.F., retired.
Oakley.—On September 4, 1955, at Combs, Chapel-en-le-Frith, Cheshire, George Gardner Oakley, M.R.C.S., L.R.C.P., formerly of Holly House, Halifax, Yorks.
Robertson.—On September 9, 1955, at Victoria Hospital, Kirkcaldy, William George Robertson, M.D., of 32, Marketgate, Crail, Fife.
Walker.—On September 13, 1955, at Lewisham Hospital, William Benjamin Walker, M.D., D.P.H., of 87, Bromley Road, Catford, London, S.E.
Youatt.—On September 8, 1955, at his home, Applegold, Little Leighs, Chelmsford, Essex, Leonard Youatt, M.B., Ch.B., D.P.H., late of Prescott, Lancs, aged 87.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Is Saccharin Quite Safe ?

Q.—*Has the long-continued use of saccharin as a sweetener for drinks been reported to have any ill effects on normal or diabetic persons ?*

A.—Pharmacological, toxicological, and clinical investigations have confirmed the fact that saccharin is a completely harmless substitute for sugar, even when used continuously. 1½ to 3 gr. (0.1–0.2 g.) saccharin is sufficient to replace the whole of the sugar required by an adult for daily sweetening of food and drink.[1] The administration of saccharin to human subjects in a dose of 50 mg. in 80 ml. of water causes a decrease of 12 to 16% in the blood sugar level of normal persons.[2] Experiments *in vitro* showed saccharin to have an anti-prothrombin effect, but ingestion of saccharin in amounts above those obtaining in ordinary use was found to be without effect on the prothrombin time. There is stated to be no synergism or antagonism between saccharin and dicoumarol.[3]

References

1 Staub, H., and Stachelin, R., *Med. Press.*, 1936, **193**, 419.
2 Kun, E., and Horvath, I., *Proc. Soc. exp. Biol. (N.Y.)*, 1947, **66**, 177.
3 Barnard, R. D., *J. Amer. pharm. Ass.*, 1947, **36**, 225.

Catheterization in General Practice

Q.—*What is the safest, least uncomfortable, and most convenient way of catheterizing a male patient under the conditions of general practice ?*

A.—There is no reason why there should be any more risks from catheterizing a patient in general practice than in hospital. Indeed, there are commonly many more dangerous pathogenic organisms in a hospital ward than in the home. For this reason, provided a sterile catheter is used with a proper technique, there should be no anxiety about passing a catheter when there are clear-cut indications for doing so.

The type of catheter to be used will depend upon circumstances and individual preference. The most common type of case in practice will be the patient with retention due to an enlarged prostate. In most of these patients a soft rubber catheter will suffice; but, if there is much enlargement of the middle lobe of the prostate, the rather firmer rubber bicoudé catheter of Tiemann may prove more useful. The latter is more likely to slip through the posterior urethra without arrest on the prominent middle lobe of the prostate. However, as the Tiemann catheter is curved at the tip and made of harder rubber it is necessary to pass it with great care and gentleness else bleeding may be caused. But whatever type of catheter is used it should be reasonably new or well cared for. It is wise to reject any catheter which has become too soft, brittle, or curled up in storage.

The simplest method of sterilization is by boiling for not less than two minutes (the catheter being placed in the already boiling water). A sterile lubricant should be liberally applied to the catheter, but unless a certainly sterile lubricant is available it is better to rely on the wetness of the catheter when taken out of the boiler (having, of course, allowed it to cool sufficiently first of all). Sterile paraffin can be kept in a screw-topped bottle in the doctor's bag, but it is important for this lubricant to be autoclaved regularly or for some reliable source of supply to be arranged.

The prepuce should be completely retracted and the glans cleaned carefully with soap and water or with 1% solution of cetrimide, all smegma being removed. In some patients with marked phimosis it is impossible to pass the catheter under conditions of adequate sterility without a dorsal slit or circumcision. To what extent it is justifiable to run the risk of infection in such cases must be decided by the individual doctor in the light of the circumstances.

It is simplest to hold the catheter at about its mid-point, if possible in a sterile swab, and to pass it with the penis held up vertically. In this position the weight of the catheter will usually allow it to pass gently through the penile urethra without the use of force. The ease with which the posterior urethra is manipulated will depend upon the degree of congestion there and the type of prostatic enlargement.

No mention has been made here of the use of a local analgesic, since it is unlikely to be very practicable in those circumstances where catheterization is most commonly needed in general practice. However, if a local analgesic is considered necessary, 2% lignocaine or 5% procaine solution may be used.

Offensive Breath in a Child

Q.—*A robust, well-grown boy of 4½ years suffers from offensive breath. There is no sign of alimentary, dental, or pulmonary disease. What is the probable aetiology, and what can be done ?*

A.—Offensive breath must necessarily be due to some disorder of the respiratory or alimentary tract, or to disease of the teeth or gums. In the ketosis due to vomiting or starvation the breath has a characteristic but not offensive smell, and this is common enough in childhood.

Upper respiratory tract infection is by far the commonest cause of offensive breath in childhood, and a chronic tonsillar infection, with pus or caseous matter well hidden in the crypts, is easily missed if attention is not called to the tonsils by obvious enlargement or inflammation. In the case described this would seem a very likely answer, particularly in view of the child's age. The soundest course of action would probably be to do nothing at all, but alternatively a second opinion on the condition of the tonsils and adenoids might be obtained.

Chronic Urticaria after Prophylactic Inoculation

Q.—*I would be most grateful for your advice on the treatment of a patient with chronic urticaria, which came on about five days after an inoculation with typhoid-paratyphoid vaccine and tetanus toxoid (T.A.B.T.). It has now persisted for three and a half months and is associated with fleeting pains which usually last about 24 hours and tend to affect mainly the wrist- and knee-joints, though the smaller joints of the hands and feet have also occasionally been stricken. Exacerbations tend to follow severe exercise, emotional stress, and the excessive consumption of alcohol. The condition is only partially controlled by antihistamine drugs, and a course of eight injections of 10 ml. of the patient's own blood at weekly intervals has had little effect. There is a past history of two previous attacks of acute urticaria lasting about three days two years ago. There was no obvious exciting cause. Three and a half years ago the patient received two T.A.B. inoculations, one year ago he received 2 ml. of antitetanus serum. There is no history of any other allergic phenomena. I presume this is a type of serum sickness, but in view of the long history I should be grateful for your advice. Would A.C.T.H. or cortisone help ?*

A.—The allergic manifestations in this case may be unrelated to the T.A.B.T. inoculation, particularly as this prophylactic does not contain any serum. Moreover, there is a history of two previous attacks of acute urticaria which did not follow inoculations of any kind.

Since antihistamine drugs have proved only partially successful in treatment, a short course of cortisone may now be justified. This drug relieves symptoms, although there is unfortunately a distinct possibility of recurrence when the administration is discontinued. It must also be borne in mind that undesirable sequelae have occurred, including

the perforation of gastric ulcers and the spread of tuberculosis. A.C.T.H. has the disadvantage over cortisone that it has to be given by injection. Neither drug should be used lightly, but only when other measures have failed. It would be advisable therefore to refer the patient to a dermatologist with experience of the local and general application of cortisone in chronic urticaria.

Disease and Fertility

Q.—*Do serious diseases, such as amoebic dysentery, affect fertility either temporarily or permanently?*

A.—Accurate studies on the effect on fertility of serious diseases are few, but there seems little doubt that in both sexes fertility may be impaired through such causes. It is certain, for example, that febrile illnesses, even of quite mild type and short duration, may lead to a marked temporary decrease in the production of spermatozoa in the male, and may temporarily inhibit ovulation in the female. The same is true of prolonged debilitating chronic infections. Although the writer is not familiar with any reports of sterility due to amoebic dysentery, there seems little reason to doubt that such a condition, particularly if accompanied by liver abscess, could very well lead to impairment of spermatogenesis in the male, and perhaps to failure of ovulation in the female.

It is uncertain whether the action of a fever on spermatogenesis, for example, usually of a temporary nature as mentioned above, may not sometimes produce irreparable damage and so lead to permanent sterility. The writer feels that this may indeed sometimes happen.

Fear of the Needle

Q.—*A young man aged 20 has a great fear of the needle. He faints in the dental chair when given a local analgesic, and the thought of a hypodermic, and more especially the taking of a sample of blood even by a needle prick, makes him go into a cold sweat, often followed by a faint. Quite a few minutes elapse before he feels normal. He is otherwise in good health and athletic. He is not afraid of being hurt and he enjoys wrestling. His mother reacts similarly. What treatment is advised?*

A.—A single phobia in an otherwise healthy young man can almost certainly be removed. His mother has a similar phobia and it is likely that he picked it up from her. As a rule the fear of an injection is connected with a dread of losing consciousness or control and has nothing to do with being hurt.

This youth should be asked by his doctor (and in his presence) to give himself an injection of a little sterile water. This simple measure can be effective in dissipating the phobia. Another plan, if a hypodermic injection is necessary, is to give 2 gr. (0.13 g.) of amylobarbitone sodium half an hour before. These indirect suggestions may fail, and, if they do, direct suggestion, with or without hypnosis, ought to be given. No doubt the groundless nature of his phobia has often been explained to him and so no further explanations are needed. Any new treatment should be started in a quiet and assured manner without preamble.

Changes in Temperature and Pulse after Fevers

Q.—*I know of several cases in which the usual range of temperature has become lower (and remained so) after a virus infection. Is this phenomenon recognized? What is the explanation, and what treatment, if any, is indicated?*

A.—Convalescence from any febrile state is often associated with an instability of the body temperature. Following influenza, for instance, convalescence may for a few days be accompanied either by the temperature ranging from 98 to 99.5° F. (36.7 to 37.5° C.), or from 96.5 to 98° F. (35.8 to 36.7° C.). The latter state, which hardly constitutes hypothermia, may be what has been observed by the questioner. Bradycardia of 50 or below is also not infrequent during the immediate post-influenzal phase. No full explanation can be offered for such alterations, though in all probability they are related to the cessation of the stimulus to metabolism which has elevated the temperature during the pyrexial phase. It is unlikely that such alterations are related in any specific way to virus infections, and in view of their generally transient nature no treatment is indicated.

Effect of High Altitude on Hypertension

Q.—*Is it harmful for people with hypertension to live at high altitudes? Many Europeans in Kenya live at altitudes between 5,000 and 10,000 ft. (1,500 to 3,000 metres) above sea level, and hypertension appears to be fairly common. In bad cases doctors advise patients to move to sea level, where they seem to improve.*

A.—One of the principal adaptations to high altitude is to increase the oxygen capacity of the blood by raising the haemoglobin content and hence the number of red blood cells. This adaptation has an important consequence: the viscosity of the blood becomes greater, and so the peripheral resistance is higher. It might be expected that the incidence of hypertension would be greater in a population at high altitude than at sea level. In fact, observers have commented on the apparent normality of acclimatized individuals as regards blood pressure. It would certainly be of great interest to have more exact information on this point. However, in view of the increased peripheral resistance entailed in adaptation, hypertensive patients should be advised not to live at high altitudes. If they are doing so, they will improve on moving to sea level.

Protein and Fat in Diets for Obesity

Q.—*In diets for obesity, can unlimited quantities of protein be given, or is there the possibility of the excess protein being split into carbohydrates and fat, as in diabetic ketosis, and deposited as fat in the tissues? Is any advantage gained by giving more than the minimum amount of fat necessary to maintain health? Please suggest a publication giving an up-to-date account of food values.*

A.—In qualitative reducing diets it is safe to allow unrestricted amounts of protein foods except milk—that is, the patient may eat as much as he likes of lean meat, fish, poultry, eggs. Milk should be limited, unless it is taken as skimmed milk, to half a pint (284 ml.) a day.

In my opinion there is no advantage gained by giving more than a minimum of fat, say 30 grammes, during the period of weight reduction.

An excellent account of the essentials of dietetics, with an appendix on food values, is contained in the *Manual of Nutrition*, published by Her Majesty's Stationery Office at 2s.

Prophylaxis in Immunized Children

Q.—*What procedure should be adopted when a child previously immunized with combined diphtheria–pertussis–tetanus vaccine (a) comes in contact wtih a case of diphtheria or pertussis; (b) sustains a dirty wound?*

A.—The practitioner would presumably be influenced by the degree of intimacy of exposure to diphtheria or pertussis, the likelihood of the wound being dangerously contaminated, and the time that has elapsed since the last inoculation. If he feels that the risk is substantial, or if he is in doubt, he should give, by the deep subcutaneous route, a booster dose of 1 ml. of the combined prophylactic, or of the specific antigen concerned (0.5 ml. in the case of diphtheria prophylactic). Should poliomyelitis be prevalent in the district, it would be wise to use toxoid preparations that do not contain alum. Further information on this subject is given in Dr. H. J. Parish's book *Antisera, Toxoids, Vaccines, and Tuberculins in Prophylaxis and Treatment* (3rd edition, Livingstone, Edinburgh and London, 1954).

Indications for Leucotomy and Prognosis

Q.—*What are the indications for leucotomy, and is any mental deterioration permanently arrested by the operation?*

A.—The indications for leucotomy are certain forms of suffering which cannot otherwise be relieved, and the operation is seldom performed unless other methods of treatment have been exhausted. The symptoms which may be relieved by it are very diverse and include: (1) physical pain (for example, from malignant disease, neuralgia); (2) severe hypochondriasis, in which the patient is disabled by pains and discomforts for which no adequate physical cause can be found; (3) unbearable tinnitus; (4) excitement and agitation arising from delusional and hallucinatory symptoms in psychotic patients; (5) chronic depression; (6) chronic and disabling obsessional states, anxiety states, states of tension. The principal effect produced by the operation is to reduce the patient's capacity to worry and ruminate about unpleasant feelings or ideas. Thus when the indication is organic pain, the patient continues to feel the pain, when present, but may cease to fear its reappearance when it has temporarily gone.

The results of the operation are also variable; defects due to excessively destructive operations and permanent damage to the personality have, however, been much less in evidence since the introduction of modified and bimedial operations. In favourable and well-chosen cases—for example, of involutional depression—there may be recovery almost up to a 100% level; as a rule, in most cases, some of the old symptoms remain, though the operation is still regarded as having been worth while. Some patients are not benefited. Mental deterioration due to progressive organic disease of the brain is, of course, not influenced by the operation.

Effect of Osteoarthritis of Hip on Knee-joint

Q.—*A patient has been advised an early arthrodesis for severe osteoarthritis of one hip, as otherwise arthritis may supervene in the corresponding knee-joint. As she is only 40 years of age she is anxious to postpone operation for a year or two. What is your opinion of the prognosis regarding the knee if operation is deferred?*

A.—There need be no fear that delaying operation will lead to the development of osteoarthritis in the corresponding knee-joint. Although osteoarthritis of the knee is occasionally coincidental with arthritis of the hip, there is no evidence that it is aggravated by the hip condition.

Pathogenicity of Streptococci and Factors Influencing It

Q.—*How can one distinguish saprophytic from pathogenic haemolytic streptococci? What determines whether a given streptococcus will cause clinical illness in an individual?*

A.—Practically all the haemolytic streptococci that produce sore throat, scarlet fever, or any of the pyogenic lesions in man belong to Lancefield's Group A; rarely they may belong to Lancefield's Groups B, C, or G. The identification of the group of a streptococcus, which is done by testing an extract of the streptococcal culture with specific antisera, is without doubt the most useful test for distinguishing the streptococci that are potentially pathogenic from those that are unlikely to produce disease. Within Group A, however, there is no satisfactory method of distinguishing the more virulent streptococci from the less virulent. The production of the so-called M antigen is not a satisfactory criterion, because many strains that are certainly virulent fail to produce it.

Among the potentially pathogenic streptococci no specific factors are known to determine the outcome of an infection. Often it must be determined by the immunity of the individual. So far as the streptococci are concerned immunity is largely type-specific, so that infection with one strain generates immunity against a second illness with other strains of the same type, but not against strains of the other 50 or more types that exist. When an individual who is a carrier of a streptococcus develops a streptococcal sore throat this is therefore probably more often due to his being infected by a new and, to him, more virulent strain than to some "activation" of the strain that he has been harbouring. The same is probably not true of streptococcal otitis media and is certainly not true of staphylococcal boils, when infection is known frequently to be with the organism that has been carried in the nose and on the skin for perhaps many months. In such cases we must presume that trauma, some other microbial invasion, or some more general physiological change allows the streptococcus or staphylococcus to invade. The idea that the organism itself has changed is also a possible explanation, but there is no direct evidence in its favour.

Time of Death in Judicial Hanging

Q.—*When does a person executed by judicial hanging actually die? Is consciousness retained for a short time after the rope has dislocated the upper cervical vertebrae?*

A.—In the published minutes of evidence given before the Royal Commission on Capital Punishment[1] the panel of prison medical officers stated that under the present method of execution death was always instantaneous as a result of fracture-dislocation of the first or second cervical vertebra, or both, with destruction of the spinal cord at the corresponding level.

REFERENCE

[1] *Report of Royal Commission on Capital Punishment, 1949-53.* 1953. H.M.S.O.

Psychological Factors in Psoriasis

Q.—*What part do psychological factors play in the aetiology of psoriasis, and how rewarding is their treatment?*

A.—A considerable number of factors may be identified as precipitating causes in psoriasis, although the essential nature of the disorder remains obscure. Among these aggravating factors psychological and psychiatric influences may be included. Their relative importance is very largely a matter of opinion, and in my own opinion not very great. It is in very few patients that psychiatric factors seem to be of great significance.

In the same way, psychiatric treatment is not usually of much direct value. It is, however, very desirable to foster the patient's morale so that he will persevere with other methods of treatment.

Correction.—The price of Sir Reginald Watson-Jones's book *Fractures and Joint Injuries*, 4th edition, in two volumes, is now £6 10s. per set, not £6 as reported in the *Journal* of September 17, page 724.

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